



DECLARATION UNDER 37 C.F.R. §1.132
Examining Group 1614
Patent Application
Docket No. UF-260XC1
Serial No. 09/997,447

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Phyllis G. Spivack
Art Unit : 1614
Applicants : Nathan Andrew Shapira, Mary Catherine Lessig, Daniel John Driscoll
Serial No. : 09/997,447
Filed : November 30, 2001
Conf. No. : 3440
For : Treatments for Neurogenetic Disorders, Impulse Control Disorders, and Wound Healing

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DECLARATION OF GREGORY W. SCHULTZ, PH.D. UNDER 37 C.F.R. §1.132

Sir:

I, Gregory W. Schultz, Ph.D., hereby declare:

THAT, I have received the following degrees:

Doctor of Philosophy 1976 Oklahoma State University, Stillwater, Oklahoma

Bachelor of Science 1971 Oklahoma State University, Stillwater, Oklahoma

THAT, I have been employed professionally as follows:

Academic Appointments

1989-present	Professor of Obstetrics/Gynecology, University of Florida, College of Medicine, Gainesville, Florida
1985-1989	Associate Professor of Ophthalmology, University of Louisville School of Medicine, Louisville, Kentucky
1985-1989	Associate Professor of Biochemistry, University of Louisville School of Medicine, Louisville, Kentucky
1979-1985	Assistant Professor of Biochemistry, University of Louisville School of Medicine, Louisville, Kentucky
1976-1979	Postdoctoral Research Associate, Yale University School of Medicine, New Haven, Connecticut
1974-1976	Graduate Student, Kansas University Medical Center, Kansas City, Kansas
1971-1974	Graduate Student, Oklahoma State University, Stillwater, Oklahoma
1967-1971	Undergraduate in Biochemistry, Oklahoma State University, Stillwater, Oklahoma

THAT, I am the Director of the Institute for Wound Research at the University of Florida and that my research focuses on the role of growth factors, cytokines and proteases in normal and chronic wound healing in the skin and in the eye. I have published over 170 research papers, chapters and review articles (a sampling of which is included on the attached Curriculum Vitae). These papers have been cited more than 4,400 times and I have multiple patents in the areas of wound healing. I was President of the Wound Healing Society from 1999-2001.

THAT, through my years of research, I have kept up to date on the technical literature and maintained contact with experts in the field by participating in professional meetings and seminars, and by direct personal contact. As a result, I am familiar with the general level of skill of those working in the field of wound healing;

THAT, I have studied application Serial No. 09/997,447, filed on November 30, 2001, the Office Actions which have been issued during prosecution of this application, the references cited in these Office Actions, and the responses which have been filed on the behalf of Applicants. Thus, being duly qualified, I declare as follows:

1. I have reviewed the disclosure of Blake *et al.* (International Application PCT /GB99/02606; International Publication No. WO 00/10610) and cannot agree with the assertion of the Patent Office that this reference would motivate one skilled in the art to use topiramate to promote wound healing. The reference is directed to the manufacture and use of bioreductive conjugates of known therapeutic agents for use in the treatment of conditions or diseases for which the therapeutic agent is recognized to be useful.

While the reference addresses or claims medicaments for "use in the healing of wounds or the treatment of fibrotic disorders", the therapeutic agents indicated as being useful in this regard are limited to growth factor neutralizing agents or agents specific against only fibrotic growth factors (see claims 2 and 3); the reference specifically speaks to neutralizing growth factors, interleukins, or other agents that are typically associated with inducing fibrosis or scarring. Specific examples of such agents that are provided in the description of Blake *et al.* are TGF- β 1; TGF- β 2; PDGF; IFN γ ; IL-1; TGF- β 3; FGF-1; FGF-2; IL-4; IL-10; betaglycan; inhibitors of: IFN- γ , at least one integrin receptor, at least one convertase enzyme, or IL-6; stimulators of: IFN- γ or activin and/or inhibin; agents that modulate actin assembly and organization, latency associated peptide; insulin like growth factor II; or compounds that influence the sex hormone system (see claims 4-21 and the description of the embodiment directed to wound healing at pages 4-14). Indeed, the description at pages 4-14 repeatedly states that the embodiments discussed on these pages are directed to wound healing (see, for example, page 7, paragraph 5; page 8, paragraphs 1 and 4; page 9, paragraphs 2 and 6; page 10, paragraph 2; page 11, paragraphs 3 and 7; page 12, paragraphs 2 and 5; page 13, paragraph 4; and page 14, paragraphs 1 and 4).

I note that topiramate is absent from the listing of agents for use in promoting the healing of wounds or the treatment of fibrotic disorders. This is not surprising as, to the best of my knowledge, there was no recognition (nor was it suspected) that topiramate had such an activity prior to the filing date of this patent application. As the Patent Office may be aware, topiramate is a drug recommended for the treatment of epilepsy (as is disclosed in the description of Blake *et al.* at page 15, paragraph 1 and the Physician's Desk Reference, a copy of which is appended hereto).

As one skilled in the art, I would not have been motivated to use topiramate for the treatment of wounds or for promoting wound healing in view of the teachings of Blake *et al.* nor would the use of topiramate for promoting wound healing be suggested to me in view of the teachings of the reference. Furthermore, as one skilled in the art, I would not, and could not, reasonably infer that the reference teaches or suggests or motivates one to use topiramate for promoting wound healing as is argued by the Patent Office.

2. As indicated above, there was, to the best of my knowledge, no recognition in the art that topiramate was useful for promoting wound healing in individuals to whom topiramate was administered and, based upon my experience in the field of wound healing, I would not have expected topiramate to provide therapeutic benefit in promoting wound healing.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Signed:

Gregory W. Schultz, Ph.D.

Date:

9-23-04

Attachments: Physician's Desk Reference (2000)
Curriculum Vitae

CURRICULUM VITAE

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Education

1971	B.S.	Honors Program in Biochemistry, Oklahoma State University, Stillwater, Oklahoma
1976	Ph.D.	Biochemistry, Oklahoma State University, Stillwater, Oklahoma Dissertation Advisor: Dr. Kurt Ebner, Regent's Professor
1979	Postdoctoral Fellow	Cell Biology, Yale University, New Haven, CT Advisor: Dr. James D. Jamieson, Professor and Chairman

Academic Appointments

1989-present	Professor of Obstetrics/Gynecology, University of Florida, College of Medicine
1985-1989	Associate Professor of Ophthalmology, University of Louisville School of Medicine
1985-1989	Associate Professor of Biochemistry, University of Louisville School of Medicine
1979-1985	Assistant Professor of Biochemistry, University of Louisville School of Medicine
1976-1979	Postdoctoral Research Associate with Dr. James D. Jamieson, Professor of Cell Biology, Yale University School of Medicine
1974-1976	Graduate student with Dr. Kurt Ebner, Professor and Chairman Department of Biochemistry, Kansas University Medical Center, Kansas City, Kansas
1971-1974	Graduate student with Dr. Kurt Ebner, Regents Professor of Biochemistry Oklahoma State University, Stillwater, Oklahoma
1967-1971	Undergraduate in Biochemistry Oklahoma State University, Stillwater, Oklahoma

Professional Societies

Phi Kappa Phi
American Society for Biochemistry and Molecular Biology
The Wound Healing Society
Association for Research in Vision and Ophthalmology

Awards and Honors

Medicinae Doctorem (honoris causa) awarded by University of Linköping, Sweden, May 1996
Everett Kinsey Lecturer of the Contact Lens Association of Ophthalmologist, January 1997
1st Ethicon Endo-Surgery Plenary Lectureship of the American Society for Reproductive Medicine, October, 1997
University of Florida Bank Research Award, 1997
Professorial Excellence Program Award, University of Florida, 1998
President of the Wound Healing Society, 1999-2001
Sustained Excellence Professors Award, University of Florida, 2001
Thygeson Lecturer of the Ocular Microbiology and Immunology Group, 2002

REFEREED PUBLICATIONS

NOTE: SCIENCE CITATION INDEX LIST 4,500 CUMULATIVE CITATIONS TO DR. SCHULTZ'S REFEREED PUBLICATIONS IN JANUARY 2002: 24 PUBLICATIONS WITH >50 CITATIONS, 10 PUBLICATIONS >100 CITATIONS, 7 PUBLICATIONS WITH >150 CITATIONS AND 3 PUBLICATIONS WITH >250 CITATIONS

1. D.W. Wesson, M.P. Popp, L. Liu, G.S. Schultz, M.B. Sherwood. Microarray Analysis of the Failure of Filtering Blebs in a Rat Model of Glaucoma Filtering Surgery. *Invest Ophthalmol Vis Sci*, in press.
2. S.A. Berceli, Z. Jiang, N.V. Klingman, C.L. Pfahnl, Z.S. Abouhamze, C.D. Frase, G.S. Schultz, C.K. Ozaki. Differential Expression and Activity of MMPs during Flow-Modulated Vein Graft Remodeling. *J Vasc Surg*, 39:1084-1090, 2004.
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9. F.J. Ollivier, D.E. Brooks, G.S. Schultz, T.D. Blalock, S.E. Andrew, A.M. Komaromy, T.J. Cutler, M.E. Lassaline, M.E. Kallberg, G.B. van Setten. Connective Tissue Growth Factor in Tear Film of the Horse: Detection, Identification and Origin. *Graefe's Archiv Clin Exp Ophthalmol*, 242:165-171, 2004.
10. F.J. Ollivier, D.E. Brooks, M.E. Kallberg, A.M. Komaromy, M.E. Lassaline, S.E. Andrew, K.N. Gelatt, G.R. Stevens, T.D. Blalock, G.B. van Setten, G.S. Schultz. Inhibition of Matrix Metalloproteinase Activities in the Tear Film of Horses With Ulcerative Keratitis, *Am J Vet Res*, 64:1081-1087, 2003.
11. J.G. Wilmoth, P.J. Antonelli, G.S. Schultz. Tympanic Membrane Metalloproteinases Inflammatory Response. *Otolaryngol Head Neck Surg*, 129:647-654, 2003.
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18. P.J. Antonelli, G.S. Schultz, D.J. Sundin, P.A. Pemberton, P.J. Barr. Protease Inhibitors Alpha-1 Antitrypsin and Ilomastat Are Not Ototoxic in the Chinchilla. *Laryngoscope*, 113:1764-1769, 2003.
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33. D.H. Lehman, P.J. Antonelli, J.G. Wilmoth, A.R. Prevatt, G.S. Schultz. Inhibition of Matrix Metalloproteinases in Gerbil Cholesteatoma. **Otolaryngol Head Neck Surg** 126:404-408, 2002.

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35. G.L. Locksmith, P. Clark, P. Duff, G.R. Saade, G.S. Schultz. Amniotic Fluid Concentrations of Matrix Metalloproteinase 9 and Tissue Inhibitor of Metalloproteinase 1 During Pregnancy and Labor. **Am J Obstet Gynecol** 184:159-164, 2001.

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37. D.T. Strubbe, D.E. Brooks, G.S. Schultz, H. Willis-Goulet, K.N. Gelatt, S.E. Andrew, M.E. Kallberg, E.O. Mackay, W.R. Collante. Evaluation of Tear Film Proteinases in Horses with Ulcerative Keratitis. **Vet Ophthalmol** 3:111-119, 2000.

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50. A. Avidano, C.S. Cotter, S.P. Stringer, G.S. Schultz. Analysis of Protease Activity in Human Otitis Media. **Otolaryngology Head Neck Surg** 119:346-351, 1998.

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53. J.W. Doyle, M.F. Smith, J.T. Garcia, G. Schultz and M.B. Sherwood. Treatment of Bleb Leaks with Transforming Growth Factor- β in the Rabbit Model. **Invest Ophthalmol Vis Sci** 38:1630-1634, 1997.

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21. S.L.D. MacKay, N.T. Bennett, K.I. Bland, G.S. Schultz. Growth Factors Tumor Suppressor and Cancer. In: **Perspectives in General Surgery**, B.A. Levine, ed. 3:1-25, 1992.
22. G.S. Schultz, D. Twardzik. Assessment Of Biological Activity Of Synthetic Fragments Of Transforming Growth Factor α . In: **Methods in Enzymology**, D Barns, J P Mather, and G H Sato, editors, Academic Press, Inc., New York NY, Vol 198, pp. 200-213, 1991
23. G.S. Schultz. Epidermal growth factor in wound healing. In: **Biological Response Modifiers for Ophthalmic Tissue Repair**, G.R. Grotendorst, L.M. Hjelmeland, and J.P. Gills, editors. Gulf Publishing Co., Houston, TX, pp. 171-182, 1990
24. G. Todaro, G.S. Schultz, D.R. Twardzik, R.A. Eiferman. Tumor Growth Factors and Vaccinia Growth Factors: Role in Epithelial Wound Healing. In: **Development and Disease of Cartilage and Bone Matrix**. Alan R. Liss, Inc., New York, p. 612, 1987.
25. R.A. Eiferman, G.S. Schultz, R.E. Nordquist. Corneal Wound Healing and its Pharmacologic Modification after Refractive Keratotomy. In: **Refractive Keratotomy for Myopia and Astigmatism**, G. O Waring, III ed., C.V. Mosby Co., St. Louis, pp. 749-779, 1991.
26. G.S. Schultz, P.W. Woost, R.A. Eiferman. Modification of Corneal Wound Healing by Growth Factors. In: **The Cornea: Transforming of the World Congress on the Cornea III**, D. Cavanaugh, ed., Raven Press, New York, NY, pp.15-21, 1988.
27. G.S. Schultz, R.A. Eiferman. Human Corneal Endothelial Mitosis and Endothelial Grafting. In: **Corneal Surgery**, F. Brightbill, ed., C.V. Mosby Co., St. Louis, pp. 613-620, 1986.

REVIEW ARTICLES

NOTE: SCIENCE CITATION INDEX LIST 575 CUMULATIVE CITATIONS TO DR. SCHULTZ'S REVIEW ARTICLES IN SEPTEMBER 2000: 5 ARTICLES >50 CITATIONS, 3 ARTICLES >100 CITATIONS, AND 1 ARTICLE >150 CITATIONS.

1. R. Lobmann, G. S. Schultz, H. Lehnert. Proteases and the Diabetic Foot Syndrome - Therapeutic Implications, **Diabetes Care**, in press.
2. G.S. Schultz, D. Barillo, D. Mozingo, G. Chin. Wound Bed Preparation and a Brief History of TIME, **International Wound J**, 1:19-32, 2004.
3. E.A. Ayello, C. Dowsett, G.S. Schultz, G. Sibbald, V. Falanga, K. Harding, M. Romanelli, M. Stacey, L. Teot, W. Vanscheidt. TIME to Prepare the Wound Bed: A New Approach to Chronic Wound Healing, **Nursing 2004**, 34:36-41, 2004.
4. G.A. Chin, G.S. Schultz, M. Stacey. Application of Wound Bed Preparation to Chronic Wound Treatments: TIME to Heal, **Primary Intention**, 11:171-187, 2003.
5. R.G. Sibbald, H. Orsted, G.S. Schultz, P. Coutts, D. Keats. Preparing The Wound Bed 2003: Focus On Infection and Inflammation, **Ostomy Wound Manag**, 49:23-51, 2003.
6. M. Lim, M.H. Goldstein, S.S. Tuli, G.S. Schultz. Growth Factor, Cytokine and Protease Interactions During

Corneal Wound Healing, **Ocular Surface** 1:53-65, 2003

7. G.S. Schultz, G. Sibbald, V. Falanga, E.A. Ayello, C. Dowsett, K. Harding, M. Romanelli, M. Stacey, L. Teot, W. Vanscheidt. Wound Bed Preparation, A Systemic Approach to Wound Bed Management. **Wound Rep Reg** 11 (sup) 1-28, 2003.
8. G. Chin, S. Gowda, G. Schultz. Evaluation of Platelet-Derived Growth Factor in a Rat Model of Ischemic Skin Wound Healing. **Wounds** 14:199-203, 2002.
9. T.D. Blalock, J.C. Varela, S. Gowda, Y. Tang, C. Chen, B.A. Mast, G.S. Schultz. Ischemic Skin Wound Healing Models in Rats. **Wounds**, 13:35-44, 2001.
10. B.A. Mast, G.S. Schultz. Growth Factors and Plastic Surgery. **J Florida Medical Association**, 86:87-91, 2000.
11. A.S. Ågren, W.H. Eaglstein, M.W.J. Ferguson, K.G. Harding, K. Moore, U.K. Saarialjo-Kere, G.S. Schultz. Causes and Effects of the Chronic Inflammation in Venous Leg Ulcers. **Acta Derm Venereol**, suppl 210:3-17, 2000.
12. M.F. Cordeiro, G.S. Schultz, R.R. Ali, S.S. Bhattacharya, P.T. Khaw. Molecular Therapy in Ocular Wound Healing. **Br J Ophthalmol**, 83:1219-1224, 1999.
13. G.S. Schultz, B.A. Mast. Molecular Analysis of the Environment of Healing and Chronic Wounds: Cytokines, Proteases and Growth Factors. **Primary Intention**, 7:7-14, 1999.
14. G.S. Schultz, B.A. Mast. Molecular Analysis of the Environment of Healing and Chronic Wounds: Cytokines, Proteases and Growth Factors. **Wounds: A Compendium of Clinical Research and Practice**, vol 10, Supplement F, 1F-10F, 1998.
15. B.A. Mast and G.S. Schultz. Interactions of Cytokines, Growth Factors, and Proteases in Acute and Chronic Wounds. **Wound Rep Reg** 4:411-420, 1996.
16. R.W. Tarnuzzer, G.S. Schultz. Biochemical Analysis of Acute and Chronic Wound Environments. **Wound Rep Reg** 4:321-325, 1996.
17. P.T. Khaw, N.L. Occleston, G. Schultz, I. Grierson, M.B. Sherwood, G. Larkin. Activation and Suppression of Fibroblast Function. **Eye** 8:188-195, 1994.
18. G.B. van Setten, G.S. Schultz, S.P. Macauley. Growth Factors in Human Tear Fluid and Lacrimal Glands. **Adv Exp Med Biol** 350:315-319, 1994.
19. G.S. Schultz, P.T. Khaw, K.W. Oxford, S.P. Macauley, G.B. van Setten, N. Chegini. Growth Factors and Ocular Wound Healing. **Eye** 8:184-187, 1994.
20. N.T. Bennett, G.S. Schultz. Growth factors and wound healing: Part II. Role in Normal and Chronic Wound Healing. **Am J Surgery** 166:74-81, 1993.
21. N.T. Bennett, G.S. Schultz. Growth factors and Wound Healing: Part I. Biochemical Properties of Growth Factors and Their Receptors. **Am J Surgery** 165:728-737, 1993.
22. G.S. Schultz, N. Chegini, M. Grant, P.T. Khaw, S.L.D. MacKay. Effect of Growth Factors On Corneal Wound Healing. **Acta Ophthalmologica**, 70:60-66, 1992.
23. G.S. Schultz, M.B. Grant. Neovascular Growth Factors. **Eye** 5:170-180, 1991.
24. G.S. Schultz, D.S. Rotatori, W. Clark. EGF and TGF- α in Wound Healing and Repair. **J Cell Biochem** 45: 346-352, 1991.
25. G.S. Schultz, J.B. Davis, R.A. Eiferman. Growth Factors and Corneal Epithelium. **Cornea** 7:96-101, 1988.

SUBMITTED PUBLICATIONS

1. L.J. McKenzie, G.S. Schultz, R.S. Williams, N.M. Dean, J.C. Varela, N. Chegini. Inhibition of Surgical Adhesions by Antisense Oligonucleotide to TGF1. Submitted
2. G.B van Setten, T Blalock, G. Grotendorst, G.S. Schultz, A. Westermark. Detection of Connective Tissue Growth Factor in Orbito-Facial Pathology. Submitted to Orbit.
3. R. Lobmann, G. Schultz, H. Lehnert. Molecular basis of wound healing in the diabetic foot syndrome. Submitted to Diabetes Care

ARTICLES IN PREPARATION

1. C. Chen, B. Michelini-Norris, S. Stevens, J. Rowsey, X. Ren, M. Goldstein, and G.S. Schultz. Quantitative Measurement of mRNAs for EGF, TGF- α , and EGF Receptor in Rat Corneas After PRK. In preparation
2. R. Leng, N. Chegini, B. Michelini-Norris, J. Rowsey, M. Goldstein, and G.S. Schultz. Immunolocalization of TGF Isoforms, TGF-II Receptor, EGF and EGF-R in Rat Corneas After PRK. In preparation
3. R. Yuan, Xio-ou Ren, T.D. Blalock, J.C. Varela, A.S. Lewin, and G.S. Schultz. Kinetic and *In Vitro* Cell Analysis of a Hammerhead Ribozyme Targeting Transforming Growth Factor Beta-1. In preparation
4. T.D. Blalock, H.V. Baker, S.S. Tuli, G.S. Schultz. Connective Tissue Growth Factor Regulation of Gene Expression in Human Corneal Fibroblasts, in preparation.

5. T.D. Blalock, H. MacArthur, G.R. Grotendorst, S.S. Tuli, M.W.J. Ferguson, and G.S. Schultz. Mannose-6 Phosphate/Insulin Like Growth Factor II Receptor Binds CTGF and Mediates Its Action on Human Corneal Fibroblasts, Submitted
6. K.B. Kim, L. Coffey, M. Goldstein, G.S. Schultz, D.W. Hahn. Analysis Of Dense Medium Light Scattering With Applications To Corneal Tissue: Experiments And Monte Carlo Simulations, submitted.
7. S.S. Tuli, R. Liu, T.D. Blalock, C. Chen, M.H. Goldstein, G.S. Schultz. Immunohistochemical Localization of TGF-a, TGF-b, EGF, and their Receptors in Rat Corneas Following PRK Ablation, in preparation.

MAJOR INVITED PRESENTATIONS

1. Identifying and Correcting the Molecular Imbalances in Chronic Wounds, World Union of Wound Healing Societies, Paris France, July 9, 2004.
2. Stem Cells in Wound Healing, Program Organizer, Symposium on Advance Wound Care, Orlando, FL, May 2, 2004.
3. Scientific Basis for Wound Bed Preparation, Wounds UK 2003, Harrogate, United Kingdom, November 12, 2003.
4. MMPs – Current Developments in Wound Biology, European J & J Wound Symposium, Hamburg, Germany, October 14 -15, 2003.
5. Future Developments in Wound Care, Innovations Seminar, Smith & Nephew, York, UK, September 25, 2003.
6. Wound Bed Preparation, European Tissue Repair Society, Amsterdam, Netherlands, September 22, 2003.
7. Scar Wars: Regulation of Ocular Scarring, Bascom Palmer Eye Institute, University of Miami, May 1, 2003.
8. Understanding the Chronic Wound, Symposium on Advanced Wound Care, Las Vegas, NV, April 28, 2003.
9. Molecular Approaches in the Treatment of Ulcerative Keratitis, Thygeson Lectureship, Ocular Microbiology and Immunology Group meeting, October 19, Orlando , FL, 2002.
10. Molecular Characterization of Acute and Chronic Wounds, 4th Australian Wound Management Association Meeting, Adelaide, Australia, March 7, 2002
11. Molecular Approaches to Regulating Ocular Wound Healing, 11th Annual European Tissue Repair Conference, Cardiff, Wales, UK, September 5, 2001
12. mRNA Responses in Rat Corneas After PRK, M. Goldstein, and G.S. Schultz, XIV International Congress of Eye Research, Santa Fe, NM, October 15-18, 2000
13. Molecular Pathophysiology of Venous Ulcers. 1st World Wound Healing Congress, Melbourne, Australia, September 11-13, 2000
14. Cytokines and Proteases in Acute and Chronic Wounds. 8th Annual Meeting of the European Tissue Repair Society, Copenhagen, Denmark, August 27, 1998.
15. Protease and Inhibitors in Corneal Wound Healing, XIII International Congress of Eye Research, Paris, France, July 27, 1998.
16. Molecular Pathophysiology of Chronic Wounds, Association of Advanced Wound Care Symposium, Miami, April 21, 1998.
17. Molecular Regulation of Wound Healing, Florida Wound Care Symposium, Gainesville, FL, February 7, 1998.
18. Gene Therapy For Acute and Chronic Wounds, Australian Wound Management Association Meeting, Brisbane, Australia, January 10, 1998.
19. Biochemical Analysis of Acute and Chronic Wounds, University of Miami, October 3, 1997.
20. Growth Factors and Wound Healing, 1st Ethicon Endo-Surgery Lectureship, American Society for Reproductive Medicine, October 21, 1997, Cincinnati, OH.
21. Corneal Wound Healing, Everett Kinsey Lecture at the annual meeting of the Contact Lens Association of Ophthalmologist, Las Vegas NV, January 16 to 18, 1997.
22. Regulation of Corneal Wound Healing by Growth Factors, Keystone Symposium on Ocular Cell and Molecular Biology, Tamarron, Colorado, January 7 to 12, 1997.
23. Differential Expression of Cytokines in Acute and Chronic Human Wounds, 4th International Congress on The Immune Consequences of Trauma, Shock, and Sepsis, March 4 to 8, 1997, Munich, Germany.
24. 3rd International Congress on Pelvic Surgery and Adhesion Prevention, February 29, 1996, San Diego, CA.
25. Modulation of Corneal Wound Healing, Oxford Ophthalmic Congress, Oxford, UK, July 2-5, 1995.
26. Modulation of Corneal Wound Healing, Joseph M. Bryan Lecturer, Duke University, January 11, 1995.
27. Protease Levels in Healing and Chronic Human Wounds. Protease and Adhesion Molecules in the Pathophysiology and Treatment of Cancer, Inflammation/Coagulation and Skin Disorders, Brodo/Ljubljana, Slovenia, June 4-8, 1994.
28. Biochemical Analysis of Human Wound Fluids. Fourth Annual Research Forum on Wound Repair, University of Miami, April 28 to May 1, 1994.
29. Biochemical Analysis of Human Wound Fluids. Medical and Dental College of New Jersey, University of New

Jersey, January 5, 1994.

30. Growth Factors and Proteases in Ocular Wound Healing. Singapore Nation Eye Center, December 13, 1993.

31. Growth Factors and Ocular Wound Healing. XXIII Cambridge Ophthalmology Symposium, September 9-10, 1993.

32. EGF and TGF- α Wound Repair, UCLA Conference on Progress in Basic Research of Wound Repair and its Application to Clinical Management of Problem Wounds. Breckenridge, CO. April 3, 1993.

33. The Use of Growth Factors in Promoting Wound Healing, Washington State Ophthalmological Society Meeting, Seattle, WA, September 21, 1991.

34. Growth Factors and Ocular Wound Healing, Wound Healing of the Ocular Surface & Paulo Foundation International Medical Symposium, Helsinki, Finland, August 25-28, 1991.

35. EGF and Wound Therapy, UCLA Symposium on Wound Repair. Keystone, CO April 7, 1991.

36. Growth Factors, 15th Clinical Congress of the American Society of Parenteral and Enteral Nutrition, San Francisco, CA, January 26, 1991.

37. Overview of Growth Factors and Wound Healing II, Technology Management Group, Boston, MA, December 6-7, 1990.

38. Neovascular Growth Factors, Cambridge Ophthalmological Symposium, St. John's College, Cambridge, England, September 17-19, 1990.

39. EGF and its Receptor in Cornea and Wound Healing. University of Kansas, April 5, 1990.

40. EGF and TGF- α in Wound Healing and Repair, UCLA Symposium on Tissue Engineering, Key Stone, CO., April 6-12, 1990.

41. Overview of Growth Factors in the Eye, Annual Meeting of the Association for Research in Vision and Ophthalmology Association, Sarasota, Florida, April 30, 1989.

42. EGF in Corneal Wound Healing, Visions in Wound Healing, March 16-18, 1988 Innisbrook, Florida.

43. Biosynthetic Growth Factors and Wound Healing, Industrial Biotechnology Association, February 16-18, 1988, Naples, Florida.

44. Modulation of Corneal Wound Healing by Growth Factors, Emory University, September 16, 1988

45. Transforming Growth Factor-Alpha (TGF- α) and its Receptor in Neural Retina. Eight International Congress for Eye Research, San Francisco, September 4-8, 1988.

46. Development of Epidermal Growth Factor and Its Uses in Wound Healing. Growth Factors for Wound Healing, symposium sponsored by Technology Management Group, Inc., New Haven, CT, November 1-3, 1988.

47. Candidate Agents to Enhance Wound Healing. American Society of Cataract and Refractive Surgery, Los Angeles, CA, March 29, 1988.

48. Molecular Mechanism of Regeneration of Wound Healing by Growth Factors. Memorial Sloan-Kettering Cancer Center, New York, NY, February 26, 1988.

49. Topical Epidermal Growth Factor. Castroviejo Society Symposium, Las Vegas, January 14, 1988.

50. Drugs That Modify Corneal Wound Healing. World Congress on the Cornea III, Washington, D.C., April 27-May 1, 1987.

51. Effect of Growth Factors in Keratorefractive Surgery. World Refractive Surgery Symposium, Rome, Italy, May 2-4, 1986.

52. Pre-Clinical Application of Biosynthetic EGF. American Tissue Culture Association. Ohio Valley Branch, Columbus, OH, April 3, 1986.

53. Hormonal Regulation of Wound Healing, Collagen Corp., San Francisco, CA, June 1, 1985.

54. Human Corneal Endothelial Cell Mitosis and Endothelial Grafting - Is it Possible in Corneal Surgery and Eye Banking. First International Cornea and Eye Banking Symposium, San Diego, CA, June 4-8, 1985.

55. Action of Growth Factors on Corneal Wound Healing. Sixth International Congress for Eye Research, Alicante, Spain, October, 1984.

56. Acceleration of Corneal Wound Healing by Biosynthetic Human EGF. University of Oklahoma, Department of Ophthalmology, March 26, 1984.

57. Role of EGF and TGF in Breast Cancer. Oncogen, March 20, 1984.

58. A Mini Symposium on Potential Application of EGF in Surgery. Chiron Corporation, February 20, 1984.

59. Peptide Growth Factors: Comparison of in vitro and in vivo effects. Ohio Valley Tissue Culture Association, Miami University, October, 1983.

60. Symposium on Renin-Angiotensin System: Enzymology, Receptor and its Role in Understanding Hypertension. University of Kentucky, April 20, 1981.

LECTURES AT THE UNIVERSITY OF LOUISVILLE

1. **Medical Biochemistry 600.** Presented lectures, from 1979 to 1989, on water, pH, amino acids, protein structure and purification, collagen, elastin, contractile proteins, blood clotting, antibodies, simple carbohydrates, proteoglycans, glycoproteins, and endocrinology. Course director, first quarter, 1984.
2. **Biochemical Endocrinology 670.** Initiated this new graduate course required for Ph.D. students in Biochemistry in 1980. Presented lectures in 1980, 81, 82, 83 on pituitary hormones including gonadotrophins, prolactin, growth hormone, ACTH, and on endorphins, growth factors, oncogenes, catecholamines, insulin, glucagon, gastrointestinal hormones and angiotensin. In 1984 this course was enlarged to include topics of advanced reproductive endocrinology including placental hormone production, immune system hormones, and biochemical aspects of in vitro fertilization/embryo transfer. Course director 1980-1988.
3. **Biochemical Methods 612.** Presented lectures, from 1979 to 1988, on radioisotopic techniques, and on cell and tissue culture techniques.
4. **Special Topics in Biochemistry 603.** Presented lectures in 1981, 82 on glycoprotein biosynthesis, and intracellular compartmentalization of proteins.
5. **Board Review Course BRC-84.** Presented review lectures on protein chemistry, hemoglobin, blood clotting and enzymology for sophomore students taking National Boards, Part I.

RESEARCH INSTRUCTION AT UNIVERSITY OF LOUISVILLE

1. Primary Advisor	Year	Current Position
Susan Fitzpatrick, M.S.	1980	Faculty member, Baylor University
William King, M.S.	1986	Resident in Surgery, University of Louisville
Philip Woost, Ph.D.	1987	Postdoctoral Associate, Case Western University
Glenn Franklin, M.S.	1988	Resident in Surgery, Medical College of Georgia
John Henry, Ph.D.	1989	Boston Biomedical Research Institute
2. DISSERTATION OR THESIS COMMITTEES	YEAR	DEPARTMENT
Ronald Wiegle, Ph.D.	1983	Biochemistry
Georgette Howard, Ph.D.	1986	Biochemistry
James Miller, Ph.D.	1987	Biochemistry
Steve Wagner, Ph.D.	1986	Biochemistry
Raymond Weckman, M.S.	1983	Anatomy
Melinda Brown, Ph.D., MD	1984	Anatomy
Nancy Muma, Ph.D.	1985	Pharmacology
Deanne Benovitz, Ph.D.	1986	Chemistry
Douglas Sherman, Ph.D.	1988	Chemistry
Patricia Drury, M.S.	1988	Anatomy
3. Postdoctoral Associates	Year	Current Position
Michael P. LaChance, MD, Ph.D.	1982	Private practice
Gerry O'Daniel, MD	1986	Private practice
Nancy Muma, PhD	1985	Pharmaceutical industry
Mindy Brown, Ph.D., MD	1985	Private practice
Elaine Sonnenfeld, Ph.D.	1986	Pharmaceutical industry
Mark Petitjean, MD	1987	Private practice
Krzysztof Darlak, Ph.D.	1987-88	Peptides International, Inc.
Shawn Jones, M.D.	1987-88	Private practice
4. Research Assistant Professor		

Dr. Ming Ling, 1983, currently Chairman of Biochemistry, National University of Taiwan

5. Medical/Dental Students: Summer Research Program or Research Elective

Larry Williams, M.D.	1983	Lisa Cipolla, M.D.	1987
Joseph Metz, DMD	1983	Angela Duff, M.D.	1987
Mark Lambertus, M.D.	1984	Allan Whitehouse, M.D.	1987
Jerry Schrodt, M.D.	1985	Robert Mitchell, M.D.	1988
Joseph Brightwell, M.D.	1985	Jerry Davis, M.D.	1988
Steve Riddle, M.D.	1986	E. Brit Brockman, M.D.	1988
John Fassio, M.D.	1989		

6. Undergraduate Summer Research Scholars

1. Jamie Monroe	1983
2. Mary Lorenz	1980
3. Melissa Roberts	1987

7. Awards Recognizing Research of Graduate or Medical Students

Philip Woost	Yankeelov Award for Outstanding Ph.D. student in Biochemistry, 1984; First Place, Student Research Day Competition, 1983; Graduate and Professional Student Research Awards, 1982 and 1983; American Cancer Society Institutional Award, 1983-84
Lisa Cipolla	Second Place, Student Research Day Competition, 1984
Angela Duff	Honorable Mention, Student Research Day Competition, 1984
Steve Riddle	Second Place, Student Research Day Competition, 1983
Jerry Schrodt	Honorable Mention, Student Research Day Competition, 1982

CLASSROOM INSTRUCTION AT THE UNIVERSITY OF FLORIDA

- BMS 5204 Medical Biochemistry.** Teach ten clinical correlation discussions for a unit lab of freshman medical students from 1991 to present.
- GM 6161 Oral Biology II.** Teach one lecture on general principles of wound healing to oral biology graduate students and post-graduate dental fellows from 1995 to present.
- DEN 6657 Introduction to Advanced Periodontology.** Teach three lectures on the principles of wound healing to oral post-graduate periodontology fellows from 1996 to present.
- GMS 6001 Interdisciplinary Graduate Program Core Course.** Teach two lectures and one discussion session on the components of the extracellular matrix in 1998-2000.
- Dentistry 6128 Principles of Immunology.** Teach three lectures on the principles of wound healing to second year dental students from 1999- to present.

RESEARCH INSTRUCTION AT UNIVERSITY OF FLORIDA**1. PRIMARY ADVISOR**

<u>PROGRAM</u>	<u>AREA</u>	<u>DEGREE</u>	<u>YEAR</u>
MS Program	Molecular Genetics	M.S.	1998
IDP Program	Cell Biology	M.S.	1999
MS Program	Molecular Genetics	M.S.	2000
MS Program	Molecular Genetics	M.S.	2000
MS Program	Molecular Genetics	M.S.	2002
APPCI	Clinical Investigation	M.S.	2002
IDP Program	Molecular Genetics	Ph.D.	2003
MS Program	Molecular Genetics	M.S.	2004
PhD Program	Molecular Genetics	Ph.D.	candidate
MS Program	Molecular Genetics	M.S.	candidate

2. M.S. & PH.D. DISSERTATION COMMITTEES	DEPARTMENT	DEGREE	YEAR
James Talton, M.S.	Material Sciences	M.S.	1995
Shawn P. Macauley, Ph.D.	Oral Biology	Ph.D.	1996
Susan Rasmussen, Ph.D.	Chemistry/Biochemistry	Ph.D.	1997
Robert Habda, M.S.	Material Sciences	M.S.	1997
Ho-Seng Kim, Ph.D.	Pharmaceutical Sciences	Ph.D.	1998
Adriana Da Silveira, Ph.D.	Oral Biology	Ph.D.	1998
Sharon Wall, Ph.D.	Neuroscience	Ph.D.	1998
James Talton, Ph.D.	Pharmaceutics	Ph.D.	1999
Larry Land, Ph.D.	Chemistry	Ph.D.	2001
Toby Ferguson, Ph.D., M.D.	Neuroscience	Ph.D.	2000
Harveen Dhillon, Ph.D.	Neuroscience	Ph.D.	2000
Sonja Parisek, M.S.	Animal Sciences	M.S.	2001
Jing Li, M.S.	Molecular Genetics	M.S.	2003
Mihai Ciustea, B.S.	Chemistry	Ph.D.	2003
Kareem Burney, B.E.	Biomedical Engineering	M.S.	2003
Taili Thula, B.E.	Biomedical Engineering	M.S.	2003
Franck Ollivier, DVM	Animal Sciences	Ph.D.	2004
Rong Xiu, B.S.	Molecular Genetics	M.S.	2004
Beverly Childress, B.S.N.	Nursing	Ph.D.	2004
John Azeke, B.E.	Biomedical Engineering	Ph.D. candidate	
Tara Washington, B.E.	Biomedical Engineering	Ph.D. candidate	
Olajompo Moloye, B.E.	Biomedical Engineering	Ph.D. candidate	
Kareem Burney, B.E., M.S.E.	Biomedical Engineering	Ph.D. candidate	
Taili Thula, B.E., M.S.E.	Biomedical Engineering	Ph.D. candidate	
Lee Ferguson, B.S.	Molecular Genetics	Ph.D. candidate	

3. EXTERNAL EXAMINER

Rijian Wang, Ph.D.	1997	University of Alberta, Edmonton, Canada Department of Surgery
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4. RESIDENTS RESEARCH PROJECTS

<u>Ophthalmology</u>	<u>Year</u>	<u>Surgery</u>	<u>Year</u>	<u>Otolaryngology</u>	<u>Year</u>
Scott Strelow, M.D.	1989	Scott Rotatori, M.D.	1989	Jonathan King, M.D.	1990
Natalie Kerr, M.D.	1990	Neil Bennett, M.D.	1990	Agnes Nall, M.D.	1992
John Barletta, M.D.	1992			Hugh Sims, M.D.	1992
Karen Oxford, M.D.	1992			Warren Stiles, M.D.	1992
Kelly Hutcheson, M.D.	1995			Peyton Colvin, M.D.	1993
Mario Forcina, M.D.	1996			Mike Avidono, M.D.	1993
Guy Angella, M.D.	1997			Cheryl Cotter, M.D.	1993
John Gross, M.D.	2002			Jason Wilmoth, M.D.	1998

6. MEDICAL STUDENTS RESEARCH ELECTIVES

Lee Jung, 1990	Kyle Balch, 1992	David Kimble, 1992	Robert Stiff, 1994	Jeff Brink, 1990
Ken Haft, 1992	Tuan Nguyen, 1993	Missy Block, 1996	Steve Tebes, 1997	

7. Post Doctoral Associate

	<u>Years</u>	<u>Current Position</u>
Sally MacKay, Ph.D.	1991-4	Assistant Professor, Dept Surgery, Univ. Florida
Roy Tarnuzzer, Ph.D.	1993-6	Assistant Professor, Dept Medicine, Univ. Florida
Xiao-ou Ren, M.D., Ph.D.	1996-8	Post-Doctoral Associate, University of North Carolina
Rong Yuan, M.D., Ph.D.	2000-1	Research Associate, Cold Springs Harbor Labs

8. HIGH SCHOOL STUDENTS AND SCIENCE TEACHERS

Tuan Lui	1995	Summer Scientists Training Program	Miami High School, Miami, Florida
David Mills	1996	Summer Scientists Training Program	Deltona High School, Deltona, Florida
Lan Van	1997	Summer Scientists Training Program	Miami High School, Miami, Florida
Dan Foster	1997	Teacher Research Update Experience	Powell High School, Knoxville, TN
Sun Hee Rim	1998	Summer Scientists Training Program	Hillsborough High School, Hillsborough, Florida
Jessica Prenatt	1998	Teacher Research Update Experience	Lovejoy Middle School, Lovejoy, GA

Pamela Smith	1998	Teacher Research Update Experience	Johnson Middle School, Jacksonville, FL
Albert Huang	1999	Summer Scientists Training Program	Spruce Creek High School, Ormond Beach, FL
Vandana Gupte	1999	Teacher Research Update Experience	Hedgesville High School, Hedgesville, WV
Alicia Wright	2000	Summer Scientists Training Program	Vanguard High School, Ocala, Florida
Mindy Pearson	2000	Teacher Research Update Experience	Rodgers Middle School, Riverview, Florida
Vikram Palkar	2001	Summer Scientists Training Program	Anderson High School, Ft. Lauderdale, Florida
Cynthia Vasques	2002	Summer Scientists Training Program	Boca Raton High School, Florida
David Reyes	2003	Summer Scientists Training Program	Blanche Ely High School, Pompano Beach, FL
Craig Levoy	2004	Summer Scientists Training Program	Spruce Creek High School, Ormond Beach, FL
Philip Carlson	2004	Summer Scientists Training Program	Christopher Columbus High School, Miami, FL

9. SENIOR UNDERGRADUATE HONORS RESEARCH PROJECTS

Eric Kohlbrenner	1998	Senior Research
Juan Varela	1999	University Scholar Program
Kelly Brinsko	2000	University Scholars Program
Kavita Gandhi	2001	University Scholars Program
Sima Patel	1999	Senior Research
Brett Baschovitz	2003	Senior Research

SERVICE AT THE UNIVERSITY OF LOUISVILLE

COLLEGE OF MEDICINE

Committee

	<u>Year</u>
1. Medical Student Grievance Committee	Member 1981-1986, Chair, 1983-86
2. Freshman Medical Student Unit Laboratory Advisor	Member 1982-84
3. J. G. Brown Cancer Center, Oncology Seminar Committee	Chair, 1983-84
4. J. G. Brown Cancer Center, Education Committee	1982
5. Medical Student Promotions Committee	1984
6. President's Distinguished Teaching Award, Medical Center	Nomination Committee, 1984-86
7. Pharmacology Graduate Program Review Committee	Chair, 1985

Biochemistry Department

1. Search Committee for Assistant Professor positions, 1981, 82, 86, 87 (Chair)
2. Director of Undergraduate Summer Research Program, 1980
3. Graduate Committee, 1979-87
4. Personnel Committee, 1984, 86, 87
5. Research Committee, 1984, 86, 87
6. Co-organizer of Research Conference, "Biochemistry of Ligand-Protein Interaction" 1979

Associate Appointments

1. Department of Ophthalmology, 1984
2. Department of Obstetrics and Gynecology, 1984
3. Department of Surgery, 1984

SERVICE AT THE UNIVERSITY OF FLORIDA

General Committees

1. Clinical Research Center, Review Committee, 1989-91
2. University of Florida Faculty Senate, 1991-1992
3. Faculty Council, Ob/Gyn Department Representative, School of Medicine, 1994-95
4. Faculty Council, Vice President, School of Medicine, 1995-96
5. Basic Science Reorganization Faculty Advisory Committee, October, 1995
6. Faculty Council, President, 1997-98
7. Faculty Research Advisory Board, 1996-99
8. Sexual Harassment Committee, 2000-present
9. Medical Student Admission Committee, 2002-2005
10. Faculty Council Secretary, 2003-2006

11. University Academic Freedom, Tenure, Professional Relations and Standards Committee, 2004-

Faculty Search Committees

1. Chair, Department of Biochemistry, May, 1995
2. Assistant Professor, Structural Biologist, Department of Ophthalmology, July 1995
3. Assistant Research Scientist, Department of Otolaryngology, August 1995.
4. Assistant Professor, Department of Physiology, 1997
5. Chief of Plastic Surgery, Department of Surgery, 2004
6. Chair, Department of Dermatology, 2004

Adjunct Faculty Appointments

1. Department of Biochemistry, 1992	3. Department of Ophthalmology, 1989
2. Department of Medicine, 1992	4. Department of Oral Biology, 1995

SERVICE FOR SCIENTIFIC ORGANIZATIONS

Scientific Organizations

1. Program Planning Committee, Association for Research in Vision and Ophthalmology, Cornea, 1988-1991
2. Board of Directors, Wound Healing Society, 1995-97.
3. Program Planning Committee, 2nd Joint Meeting of Wound Healing Society and European Tissue Repair Society, Boston MA, May, 1996.
4. President-Elect of Wound Healing Society, 1997-98
5. President of Wound Healing Society, 1999-01
6. Past President of Wound Healing Society, 2000-2002

Ad Hoc Reviewer

Journals

1. American Journal of Surgery	15. Federation Proceedings
2. American Journal of Physiology	16. Infection and Immunity
3. American Journal of Pathology	17. Investigative Ophthalmology and Visual Science
4. Biochimica et Biophysica Acta	18. Journal of Investigative Dermatology
5. Breast Cancer Research and Treatment	19. Journal of Histochemistry and Cytochemistry
6. British Journal of Ophthalmology	20. Journal of Surgical Research
7. Cancer Research	21. Journal of Interferon Research
8. Cell and Molecular Biology	22. Journal of Vascular Surgery
9. Comparative Biochemistry and Physiology	23. Molecular Pharmacology
10. Current Eye Research	24. Molecular and Cellular Biochemistry
11. Diabetologia	25. Proceedings of the National Academy of Science
12. Diabetes Care	26. Regulatory Peptides
13. Endocrinology	27. Society for Experimental Biology and Medicine
14. Experimental Eye Research	28. Wound Repair and Regeneration

Editorial Board

Executive Editor for Experimental Eye Research, 1997 – present

Editorial Board for Current Eye Research, 2001 – present

Cutaneous and Ocular Toxicology, 2001 – present

Primary Intention, Australian Wound Management Association, 2002 – present

Wound Repair and Regeneration, 2002 – present

International Wound Journal, 2003 – present

International Journal of Lower Extremity Ulcers, 2004 – present

REVIEWER FOR GRANT AGENCIES

1. Kentucky Heart Association 1985
2. National Science Foundation 1986
3. NIH Vision 1 Study Section Ad Hoc member 1988
4. NIH Institute of Arthritis Musculoskeletal Disease Ad Hoc member 1991

5. NIH Clinical Sciences 1 Study Section Ad Hoc member 1992
6. Tobacco and Health Research 1988
7. W. W. Smith Charitable Trust 1992
8. Wellcome Trust, Ltd 1993
9. NIH Arthritis, Connective Tissue and Skin Study Section Ad Hoc member 2004

Patents Awarded and Submitted

1. Promotion of Corneal Stroma Wound Healing With Human Epidermal Growth Factor Prepared From Recombinant DNA. Inventors: G.S. Schultz, R.A. Eiferman, G.L. Brown, assigned to University of Louisville, and P. Valenzuela, assigned to Chiron Corporation, U.S. Patent No. 4,959,353, issued September 25, 1990.
2. Treatment for Tissue Ulceration. Inventors: R.E. Galardy, D. Grobelny, G.S. Schultz assigned to University of Florida. U.S. Patent No. 5,114,953, issued May 19, 1992.
3. Treatment for Tissue Ulceration. Inventors: R.E. Galardy, D. Grobelny, G.S. Schultz assigned to University of Florida. U.S. Patent No. 5,270,326, issued December 14, 1993.
4. Method for Treating Corneal Endothelial Wounds. Inventors: G.S. Schultz, assigned to University of Florida and R.W. Shimuzu assigned to Chiron Vision. U.S. Patent No. 5,310,728, issued May 10, 1994.
5. Synthetic Matrix Metalloproteinase Inhibitors and Use Thereof. Inventors: R.E. Galardy, D. Grobelny, G. Schultz assigned to University of Florida. U.S. Patent No. 5,773,438, issued June 30, 1998.
6. Process for Preparing Synthetic Matrix Metalloprotease Inhibitors. Inventors G. Schultz, assigned to the University of Florida. U.S. Patent No. 5,892,112; issued April 6, 1999.
7. Medical Use of Metalloproteinase Inhibitors for Inhibiting Tissue Contraction. Inventors: P.T. Khaw, assigned to University of London, and G.S. Schultz assigned to University of Florida. U.S. Patent No. 6,093,398 issued July 25, 2000.
8. Medical Use of Metalloproteinase Inhibitors for Inhibiting Tissue Contraction. Inventors: P.T. Khaw, assigned to University of London, and G.S. Schultz assigned to University of Florida. U.S. Patent No. 6,379,667 issued April 30, 2002.
9. Cosmetic Composition and Method. Inventors: G.S. Schultz, assigned to University of Florida, and D.S. Lerner, assigned to QuickMed Technologies. US Patent No. 6,713,074, issued March 30, 2004.
10. Intrinsically Bactericidal Absorbent Dressing and Method of Fabrication. Inventors: C.D. Batich, G.S. Schultz, B.A. Mast, assigned to University of Florida, G.M. Olderman, D. Lerner, assigned to QuickMed Technologies, Australian Patent No. 773532, issued May 27, 2004.
11. Medical Use of Metalloproteinase Inhibitors for Inhibiting Tissue Contraction. Inventors: P.T. Khaw, assigned to University of London, and G.S. Schultz assigned to University of Florida. U.S. Patent No. 6,759,432 B2, issued July 6, 2004.
12. Composition and Method for Minimizing or Avoiding Adverse Effects of Vesicants. Inventors D. S. Lerner, assigned to QuickMed Technologies, and G. S. Schultz, assigned to University of Florida. US Patent Application 2003/0083321 A1, submitted September 25, 2002.

Consultant Activities

Chiron, Inc.	Chiron Vision	Ethicon, Inc.	U.S. Biomaterials	Santen Inc.
Oncogen, Inc.	Glycomed, Inc.	Vistacon, Inc.	Anamed, Inc.	Thermogenesis, Inc.
Arriva Pharmaceuticals	Quick Med, Inc.	Fibrogen, Inc.	Renovo, Ltd.	Greystone Medical, Inc.

Clinical Trials

1. Accelerated Corneal Epithelial Wound Healing using Human Epidermal Growth Factor after Corneal Transplantation. June 1, 1984.
2. Use of Human Epidermal Growth Factor in Severe Corneal Epithelial Defects. June 10, 1984.
3. Use of Biosynthetic Human Epidermal Growth Factor for Accelerating Epidermal Healing of Split-Thickness Donor-Sites of Burn Patients. June 2, 1986.
4. Treatment of Diabetic Foot Ulcers with a Protease Inhibitor, Doxycycline, October 1, 2001.
5. Treatment of Diabetic Foot Ulcers with an Adenovirus Vector expressing PDGF, August, 2002.



PHYSICIANS' DESK REFERENCE®

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Director of Product Management: Mark A. Friedman

Associate Product Manager: Bill Shaughnessy

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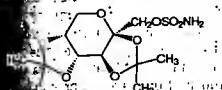


Printed on recycled paper

ISBN: 1-56363-330-2

Armaceutical, McNEILAB, Inc.
PA 19477
1997 643-10-089-2
Product Identification Guide, page 329

AMC **B**
100 mg. 60 capsules
in capsules:
capsules
ACTION: The sulfamate-substituted monosaccharide that is used as an antiepileptic drug. TOPAMAX® (capsules) Sprinkle Capsules are available as 15 mg sprinkle capsules for oral administration as a powder for opening and sprinkling onto soft food. The white crystalline powder with a bitter taste is most soluble in alkaline solutions containing carbonate or sodium phosphate and having a pH of 6.0 or greater, soluble in acetone, chloroform, dimethyl sulfoxide, and ethanol. The solubility in water is 9.8 mg/100 mL solution has a pH of 6.3. Topiramate has the formula $C_9H_{12}NO_3S$ and a molecular weight of 212.2. Topiramate is designated chemically as 2,3,4,5-tetrahydro-3-D-fructopyranose sulfamate and has the formula:



(10) aspirinate capsules) Sprinkle Capsules contain coated beads in a hard, gelatin capsule. The ingredients are: sugar spheres (sucrose and starch), cellulose acetate, gelatin, silicone dioxide, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical carbon.

PHARMACOLOGY

mechanism by which topiramate exerts its anticonvulsant effect is unknown; however, electrophysiological and biochemical studies of the effects of topiramate on culminative studies have revealed three properties that may contribute to topiramate's antiepileptic efficacy. First, action potentials elicited repetitively by a sustained depolarization are blocked by topiramate in a time-dependent manner, suggestive of a state-dependent sodium channel action.¹² Second, topiramate increases the frequency of γ -aminobutyrate (GABA) activates GABA_A receptors and enhances the ability of GABA to induce a flux of ions into neurons, suggesting that topiramate augments the activity of this inhibitory neurotransmitter but is not blocked by flumazenil, s benzodiazepine receptor antagonist.¹³ Third, topiramate increases the duration of the anticonvulsant effect by differentiating topiramate from barbiturates by modulating GABA_A receptors. Third, topiramate also modulates the ability of kainate to activate the kainate receptor (5-hydroxy-5-methylisoxazole-4-propionate, MK-4A) subtype of excitatory amino acid (glutamate) receptor but has no apparent effect on the activity of the N-methyl-D-aspartate (NMDA) at the NMDA receptor subunit. The anticonvulsant effects of topiramate are concentration-dependent, in the range of 1 μM to 200 μM . Topiramate also inhibits some isoenzymes of carbonic anhydrase (II and CA-IV). This pharmacologic effect is general to that of acetazolamide, a known carbonic anhydrase inhibitor and is not thought to be a major contributor to topiramate's antiepileptic activity.

ulation is bioequivalent to the immediate-
release formulation, and, therefore, may be substi-
tuted for it. Topiramate is rapid, with peak plasma concen-
tration at approximately 2 hours following a 400 mg dose.
The relative bioavailability of topiramate from the
extended-release formulation is about 80% compared to a solution.
The bioavailability of topiramate is not affected by food.
The pharmacokinetics of topiramate are linear with dose.
The rate of increase in plasma concentration over the
first 24 hours is (200 to 800 mg/day). The mean plasma half-life is 21 hours after single or multiple doses.
The steady state is thus reached in about 4 days in patients with normal function. The plasma is 12 to 17 mg/L.

Table 1: Topiramate Dose Summary During the Stabilization Periods of Each of Five Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Dose Stabilization	Placebo ^a	Target Topiramate Dosage (mg/day)				
			200	400	600	800	1,000
YD	N	42	42	40	41	—	—
	Mean Dose	5.9	200	390	556	—	—
	Median Dose	6.0	200	400	600	800	1,000
YE	N	44	—	—	40	45	40
	Mean Dose	9.7	—	—	544	739	796
	Median Dose	10.0	—	—	600	800	1,000
Y1	N	23	—	19	—	—	—
	Mean Dose	3.8	—	395	—	—	—
	Median Dose	4.0	—	400	—	—	—
Y2	N	30	—	—	28	—	—
	Mean Dose	5.7	—	—	622	—	—
	Median Dose	6.0	—	—	600	—	—
Y3	N	28	—	—	—	25	—
	Mean Dose	7.9	—	—	—	568	—
	Median Dose	8.0	—	—	—	600	—

*Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol Y1, 4 tablets/day; Protocol Y2, 6 tablets/day; Protocol Y3, 8 tablets/day; Protocol Y4, 10 tablets/day.

Table 2: Median Percent Seizure Rate Reduction and Percent Responders in Five Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Efficacy results	Placebo	Target Topiramate Dosage (mg/day)				
			200	400	600	800	1,000
YD	N	45	45	45	46	46	47
	Mean % Reduction	11.6	27.2 ^a	47.5 ^b	44.7 ^c	44.7 ^c	47.0 ^c
	% Responders	18	24	44 ^d	46 ^d	46 ^d	47 ^d
YE	N	47	—	10 ^e	48 ^e	48 ^e	47 ^e
	Median % Reduction	1.7	—	—	40.8 ^f	41.0 ^f	36.0 ^f
	% Responders	13	9	—	40 ^f	41 ^f	36 ^f
Y1	N	24	—	23 ^g	—	—	—
	Median % Reduction	1.1 ^g	—	40.7 ^g	—	—	—
	% Responders	8	—	35 ^g	—	—	—
Y2	N	30	—	—	30 ^h	—	—
	Median % Reduction	-12.2	—	—	46.4 ^h	—	—
	% Responders	10	—	—	47 ^h	—	—
Y3	N	28	—	—	—	28 ^h	—
	Median % Reduction	-20.6	—	—	—	24.3 ^h	—
	% Responders	0	—	—	—	43 ^h	—

Comparisons with placebo: ^ap = 0.080; ^bp ≤ 0.010; ^cp ≤ 0.001;
^dp ≤ 0.050; ^ep = 0.066; ^fp ≤ 0.005.

lation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in humans following oral administration.

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized under PRECAUTIONS (Table 3).

Special Populations:

Renal impairment: The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30–60 mL/min/1.73m²) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m²) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m²). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, use of one-half the usual dose is recommended in patients with moderate or severe renal impairment.

Topiramate is cleared by hemodialysis. Using a high efficiency, counterflow, single pass-dialysate hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20-30 mL/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialysis treatment period. Therefore, a supplemental dose may

Age, Gender, and Race:

Clearance of topiramate was not affected by age (18-67 years), gender, or race.

Pediatric Pharmacokinetics: Pharmacokinetics of topiramate

Pharmacokinetics of topiramate were evaluated in patients ages 4 to 17 years receiving one or two other antiepileptic drugs. Pharmacokinetic profiles were obtained after one week at doses of 1, 3, and 9 mg/kg/day. Clearance was independent of dose. Although the relationship between age and clearance among patients of pediatric age has not been systematically evaluated, it appears that the weight adjusted clearance of topiramate is 60% higher in pediatric patients than in adults.

CLINICAL STUDIES

The studies described in the following section were conducted using TOPAMAX® (topiramate) Tablets. The effectiveness of topiramate as an adjunctive treatment for partial onset seizures was established in five multicenter, randomized, double-blind, placebo-controlled trials, two comparing several dosages of topiramate and placebo, and three comparing a single dosage with placebo, in patients with a history of partial onset seizures, with or without secondarily generalization.

Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® Tablets or placebo. In each study, patients were stabilized on optimum dosages of their concomitant AEDs during an 8-12 week baseline phase. Patients who experienced at least 12 (or 8; for 8-week baseline studies) partial onset seizures, with or without secondarily generalization, during the baseline phase were randomly assigned to placebo or a specified dose of TOPAMAX® Tablets in addition to their other AEDs. Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. After titration, patients entered an 8 or 12-week stabilization period. The numbers of patients ran-

Topamax—Cont.

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. Responder rate (fraction of patients with at least a 50% reduction) was also measured. The median percent reductions in seizure rates and the responder rates by treatment group for each study are shown in Table 2. [See table 2 on previous page]

Subset analyses of the antiepileptic efficacy of TOPAMAX® Tablets in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

INDICATIONS AND USAGE

TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for the treatment of adults with partial onset seizures.

CONTRAINDICATIONS

TOPAMAX® (topiramate capsules) Sprinkle Capsules are contraindicated in patients with a history of hypersensitivity to any component of this product.

WARNINGS**Withdrawal of AEDs**

Antiepileptic drugs, including TOPAMAX®, should be withdrawn gradually to minimize the potential of increased seizure frequency.

Cognitive/Neuropsychiatric Adverse Events

Adverse events most often associated with the use of TOPAMAX® were central nervous system-related. The most significant of these can be classified into two general categories: 1) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties and 2) somnolence or fatigue. Additional nonspecific CNS effects occasionally observed with topiramate as add-on therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances (e.g., irritability and depression).

Reports of psychomotor slowing, speech and language problems, and difficulty with concentration and attention were common. Although in some cases these events were mild to moderate, they at times led to withdrawal from treatment. The incidence of psychomotor slowing is only marginally dose-related, but both language problems and difficulty with concentration or attention clearly increased in frequency with increasing dosage in the five double-blind trials (see **ADVERSE REACTIONS, Table 5**).

Somnolence and fatigue were the most frequently reported adverse events during clinical trials with TOPAMAX®. These events were generally mild to moderate and occurred early in therapy. While the incidence of somnolence does not appear to be dose-related, that of fatigue increases at dosages above 400 mg/day.

Sudden Unexplained Death in Epilepsy (SUDEP)

During the course of premarketing development of TOPAMAX® (topiramate) Tablets, 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2,796 subject years of exposure).

This represents an incidence of 0.0035 deaths per patient year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving TOPAMAX® (ranging from 0.0005 for the general population of patients with epilepsy, to 0.003 for a clinical trial population similar to that in the TOPAMAX® program, to 0.005 for patients with refractory epilepsy).

PRECAUTIONS**General:****Kidney Stones**

A total of 322,086 (1.5%) of patients exposed to topiramate during its development reported the occurrence of kidney stones, an incidence about 2-4 times that expected in a similar, untreated population. As in the general population, the incidence of stone formation among topiramate treated patients was higher in men.

An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a weak carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of TOPAMAX® with other carbonic anhydrase inhibitors may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

Paresthesia

Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®.

Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required (see **DOSAGE AND ADMINISTRATION**).

Information for Patients:

Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation (see **PRECAUTIONS: General**, for support regarding hydration as a preventative measure).

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

Please refer to the end of the product labeling for important information on how to take TOPAMAX® (topiramate capsules) Sprinkle Capsules.

Drug Interactions:**Antiepileptic Drugs**

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized in the following table:

In Table 3, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX® was given alone.

Table 3: Summary of AED Interactions with TOPAMAX®

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase ^a	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide ^b	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE

^a = Plasma concentration increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin.

^b = Is not administered but is an active metabolite of carbamazepine.

NC = Less than 10% change in plasma concentration.

AED = Antiepileptic drug.

NE = Not Evaluated.

Other Drug Interactions

Digoxin: In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established.

CNS Depressants: Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In a pharmacokinetic interaction study with oral contraceptives using a combination product containing norethindrone and ethinyl estradiol, TOPAMAX® did not significantly affect the clearance of norethindrone.

The mean oral clearance of ethinyl estradiol at 800 mg/day dose was increased by 47% (range: 13-107%). The mean total exposure to the estrogenic component decreased by 18%, 21%, and 30% at daily doses of 200, 400, and 800 mg/day, respectively. Therefore, efficacy of oral contraceptives may be compromised by topiramate. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns. The effect of oral contraceptives on the pharmacokinetics of topiramate is not known.

Others: Concomitant use of TOPAMAX®, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided.

Laboratory Tests: There are no known interactions of topiramate with commonly used laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 0.5 to 1 times steady state exposures measured in patients receiving topiramate monotherapy at the recommended human dose (RHD) of 400 mg, and 1.5 to 2 times steady state topiramate exposures in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 3 times the RHD on a

lymphoma assay; it did not increase unscheduled DNA synthesis in rat hepatocytes *in vitro*; and it did not induce chromosomal aberrations in human lymphocytes *in vitro*. No adverse effects on male or female fertility were seen in rats at doses up to 100 mg/kg (2.5 times the RHD on a mg/m² basis).

Pregnancy: Pregnancy Category C.

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animals. When oral doses of 20, 100, or 500 mg/kg were administered to pregnant mice during the period of organ formation, the incidence of fetal malformations (primarily craniofacial) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD) on a mg/m² basis. Fetal body weights and ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg, 2.5, 30 and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased in the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m² basis) or greater during the organ formation period of pregnancy. Embryotoxicity (reduced fetal weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m² basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater. In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 100 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m² basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (3 times the RHD on a mg/m² basis). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above. When females were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 times the RHD on a mg/m² basis) and reductions in pre- and/or post-weaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m² basis) and above.

Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater.

In a rat embryo/fetal development study with a single component (0.2, 2.5, 30 or 400 mg/kg during organ formation, noted above), pups exhibited delayed physical development at 400 mg/kg (10 times the RHD on a mg/m² basis) and consistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m² basis) and higher.

There are no studies using TOPAMAX® in pregnant women. TOPAMAX® should be used during pregnancy if the potential benefit outweighs the potential risk to the fetus.

In post-marketing experience, cases of hypospadias have been reported in male infants exposed *in utero* to topiramate, with or without other anticonvulsants; however, causal relationship with topiramate has not been established.

Labor and Delivery:

In studies of rats where dams were allowed to deliver naturally, no drug-related effects on gestation length or parturition were observed at dosage levels up to 200 mg/kg. The effect of TOPAMAX® on labor and delivery in humans is unknown.

Nursing Mothers:

Topiramate is excreted in the milk of lactating rats. It is not known if topiramate is excreted in human milk. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to TOPAMAX® is unknown, the potential benefit to the mother should be weighed against the potential risk to the infant when considering recommendations regarding nursing.

Pediatric Use:

Safety and effectiveness in children have not been established. The pharmacokinetic profile of TOPAMAX® was studied in patients between the ages of 4 and 17 years.

CLINICAL PHARMACOLOGY; Pediatric Pharmacokinetics:

Geriatric Use:

In clinical trials, 2% of patients were over 60. No age related difference in effectiveness or adverse effects were seen. There were no pharmacokinetic differences related to age alone, although the possibility of age-associated renal impairment should be considered.

Race and Gender Effects:

Evaluation of efficacy and safety in clinical trials has shown no race or gender related effects.

ADVERSE REACTIONS

The data described in the following section were obtained using TOPAMAX® (topiramate) Tablets.

The most commonly observed adverse events associated with the use of topiramate at dosages of 200 to 400 mg/day in controlled trials, that were seen at greater frequency in topiramate-treated patients and did not appear to be dose-related were: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slow-

problems, anxiety, mood problems, cognitive problems, otherwise specified, weight decreased, and tremor (see Table 5). In controlled clinical trials, 11% of patients receiving topiramate 200 to 400 mg/day as adjunctive therapy discontinued the drug due to adverse events. This rate appeared to increase at doses above 400 mg/day. Adverse events associated with discontinuing therapy included somnolence, dizziness, anxiety with concentration or attention, fatigue, and headache and increased at dosages above 400 mg/day. Approximately 28% of the 1,715 individuals with epilepsy discontinued topiramate at dosages of 200 to 1,600 mg/day. Clinical studies discontinued treatment because of adverse events; an individual patient could have reported more than one adverse event.

Adverse events were: psychomotor slowing (4.1%), difficulty with memory (3.3%), fatigue (3.3%), confusion (3.2%), headache (3.2%), difficulty with concentration/attention (2.9%), depression (2.6%), dizziness (2.6%), somnolence (2.5%), nervousness (2.2%), ataxia (2.2%), headache (2.0%), and language problems (2.0%).

Adverse Events in Controlled Clinical Trials—Add-On Therapy

Lists treatment-emergent adverse events that occurred at least 1% of patients treated with 200 to 400 mg/day topiramate in controlled trials that were numerically more common at this dose than in the patients treated with placebo. In general, most patients who experienced adverse events during the first eight weeks of these trials no longer experienced them by their last visit.

Prescriber should be aware that these data were obtained when TOPAMAX® was added to concurrent antiepileptic therapy and cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly cited frequencies cannot be directly compared with those obtained from other clinical investigations involving different treatments, uses, or investigators. Inspection of frequencies, however, does provide the prescribing physician with a basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

[Table 4 above]

[Table 5 at top of next page]

Adverse Events Observed

Events that occurred in more than 1% of patients treated with 200 to 400 mg of topiramate in placebo-controlled trials but with equal or greater frequency in the placebo group were: fatigue, headache, injury, anxiety, rash, convulsions aggravated, coughing, gastroenteritis, rhinitis, pain, hot flushes, bronchitis, abnormal gait, involuntary muscle contractions, and epistaxis.

Adverse Events Observed During All Clinical Trials

Initiated as adjunctive therapy, has been administered to 1,715 patients with epilepsy during all clinical trials. During these studies, all adverse events were reported by the clinical investigators using terminology of their choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART® dictionary terminology. The frequencies presented represent the proportion of 1,715 topiramate-treated patients who experienced an event of the type cited on at least one occasion during topiramate. Reported events are included in those already listed in the previous table, those too numerous to be informative, and those not reasonably associated with the use of the drug.

Events are classified within body system categories and listed in order of decreasing frequency using the following definitions: **frequent** occurring in at least 1/100 patients; **infrequent** occurring in 1/100 to 1/1000 patients; **rare** occurring in fewer than 1/1000 patients.

Central Nervous System Disorders: Infrequent: vasodilation, headache, dizziness, somnolence, fatigue, fever, malaise. **Central Nervous System Disorders: Rare:** ataxia, syncope, halitosis, abdomen enlarged. **Rare:** alcohol tolerance, substernal chest pain, sudden death.

Cardiac Disorders, General: **Infrequent:** hypertension, tachycardia, postural hypotension.

Cardiac & Peripheral Nervous System Disorders: **Infrequent:** hypokinesia, vertigo, stupor, convulsions, grand mal, ataxia, hypertension. **Infrequent:** leg cramps, hyporesponsiveness, migraine, apraxia, hyperesthesia, dysarthria, hyperreflexia, dysphonia, scotoma, ptosis, dystonia, field defect, coma, encephalopathy, fecal incontinence, upper motor neuron lesion. **Rare:** cerebellar syndrome, ECG abnormal, tongue paralysis.

Endocrine Disorders: **Infrequent:** goiter. **Rare:** thyroid dysfunction, hypothyroidism.

Gastrointestinal System Disorders: **Frequent:** diarrhea, constipation, gastroenteritis. **Infrequent:** gum hyperplasia, hemorrhoids, tooth caries, stomatitis, dysphagia, gastritis, saliva increased, hiccup, gastroesophageal reflux, tongue edema, esophagitis. **Rare:** eructation.

Ear and Vestibular Disorders: **Frequent:** tinnitus, headache, hyperacusis.

Cardiac and Rhythm Disorders: **Frequent:** palpitation.

Cardiac and Rhythm Disorders: **Frequent:** palpitation, tachycardia, AV block, bradycardia, bundle branch block, arrhythmia, arrhythmia atrial, fibrillation atrial.

Urinary System Disorders: **Infrequent:** SGPT increased.

Table 4: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials^{a,b}
(Events that occurred in at least 1% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients)

Body System/ Adverse Event ^c	TOPAMAX® Dosage (mg/day)		
	Placebo (N=174)	200-400 (N=113)	600-1,000 (N=247)
Body as a Whole - General Disorders			
Asthenia	1.1	8.0	4.5
Back Pain	4.0	6.2	2.0
Chest Pain	2.3	4.4	2.0
Influenza-Like Symptoms	2.9	3.5	3.2
Leg Pain	2.3	3.5	2.4
Hot Flushes	1.7	2.7	0.8
Body Odor	0.0	1.8	0.0
Edema	1.1	1.8	1.2
Rigors	0.0	1.8	0.4
Central & Peripheral Nervous System Disorders			
Dizziness	14.4	28.3	32.4
Ataxia	6.9	21.2	17.0
Speech Disorders/ Related Speech Problems	2.9	16.8	13.8
Nystagmus	11.5	15.0	15.0
Paresthesia	3.4	15.0	14.6
Tremor	6.3	10.6	13.8
Language Problems	0.6	6.2	11.7
Coordination Abnormal	1.7	5.3	3.6
Hypoesthesia	1.1	2.7	0.8
Gastrointestinal System Disorders			
Nausea	6.3	11.5	13.8
Dyspepsia	5.2	8.0	5.7
Abdominal Pain	2.9	5.3	7.3
Constipation	0.6	5.3	3.2
Dry Mouth	1.1	2.7	3.2
Gingivitis	0.0	1.8	0.4
Hearing and Vestibular Disorders			
Hearing Decreased	1.1	1.8	1.6
Metabolic and Nutritional Disorders			
Weight Decrease	2.3	7.1	12.6
Musculoskeletal System Disorders			
Myalgia	1.1	1.8	1.2
Platelet, Bleeding and Clotting Disorders			
Epistaxis	1.1	1.8	0.8
Psychiatric Disorders			
Somnolence	10.3	30.1	25.9
Psychomotor Slowing	2.3	16.8	25.1
Nervousness	7.5	15.9	20.6
Difficulty with Memory	2.9	12.4	12.6
Confusion	5.2	9.7	15.0
Depression	6.3	8.0	13.4
Difficulty with Concentration/Attention	1.1	8.0	15.4
Anorexia	4.0	5.3	11.3
Agitation	1.7	4.4	4.0
Mood Problems	1.7	3.5	10.1
Aggressive Reaction	0.6	2.7	4.0
Apathy	0.0	1.8	4.5
Depersonalization	0.6	1.8	1.6
Emotional Lability	1.1	1.8	2.4
Reproductive Disorders, Female	(N=39)	(N=24)	(N=42)
Breast Pain, Female	0.0	8.3	0.0
Dysmenorrhea	2.6	8.3	0.0
Menstrual Disorder	0.0	4.2	0.0
Respiratory System Disorders			
Upper Respiratory Infection	11.5	12.4	12.1
Pharyngitis	2.9	7.1	2.8
Sinusitis	4.0	4.4	4.0
Dyspnea	1.1	1.8	3.2
Skin and Appendages Disorders			
Rash	4.0	4.4	3.2
Pruritus	1.1	1.8	3.2
Sweating Increased	0.0	1.8	0.4
Urinary System Disorders			
Hematuria	0.6	1.8	0.8
Vision Disorders			
Diplopia	6.3	14.2	14.6
Vision Abnormal	2.9	14.2	10.5
Eye Pain	1.1	1.9	2.0
White Cell and Res Disorders			
Leukopenia	0.6	2.7	1.6

^a Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX® or placebo.

Topamax—Cont.

tase increased, dehydration, hypocalcemia, hyperlipidemia, acidosis, hyperglycemia, creatinine increased, hyperchloremia, xerophthalmia. *Rare:* diabetes mellitus, hypernatremia, abnormal serum folate, hyponatremia, hypcholesterolemia, hypoglycemia, hypophosphatemia.

Musculoskeletal System Disorders: *Frequent:* arthralgia, muscle weakness. *Infrequent:* arthrosis, osteoporosis.

Myo-, Endo-, Pericardial & Valve Disorders: *Infrequent:* angina pectoris.

Neoplasms: *Infrequent:* basal cell carcinoma, thrombocytopenia. *Rare:* polycythemia.

Platelet, Bleeding, and Clotting Disorders: *Infrequent:* gingival bleeding, purpura, thrombocytopenia, pulmonary embolism.

Psychiatric Disorders: *Frequent:* insomnia, personality disorder, impotence, hallucination, euphoria, psychosis, libido decreased, suicide attempt. *Infrequent:* paranoid reaction, appetite increased, delusion, paranoia, delirium, abnormal dreaming, neurosis. *Rare:* libido increased, manic reaction.

Red Blood Cell Disorders: *Frequent:* anemia. *Rare:* marrow depression, pancytopenia.

Reproductive Disorders, Female: *Frequent:* intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis, amenorrhea.

Reproductive Disorders, Male: *Infrequent:* ejaculation disorder, breast discharge.

Respiratory System Disorders: *Frequent:* coughing, bronchitis. *Infrequent:* asthma, bronchospasm. *Rare:* laryngitis.

Skin and Appendages Disorders: *Frequent:* acne, alopecia. *Infrequent:* dermatitis, nail disorder, folliculitis, dry skin, urticaria, skin discoloration, eczema, photosensitivity reaction, erythematous rash, seborrhea, sweating decreased, abnormal hair texture. *Rare:* chloasma.

Special Senses Other, Disorders: *Frequent:* taste perversion. *Infrequent:* taste loss, parosmia.

Urinary System Disorders: *Frequent:* urinary tract infection, micturition frequency, urinary incontinence, dysuria, renal calculus. *Infrequent:* urinary retention, face edema, renal pain, nocturia, albuminuria, polyuria, oliguria.

Vascular (Extracardiac) Disorders: *Infrequent:* flushing, deep vein thrombosis, phlebitis. *Rare:* vasospasm.

Vision Disorders: *Frequent:* conjunctivitis. *Infrequent:* abnormal accommodation, photophobia, abnormal lacrimation, strabismus, color blindness, myopia, mydriasis. *Rare:* cataract, corneal opacity, iritis.

White Cell and Reticuloendothelial System Disorders: *Infrequent:* lymphadenopathy, eosinophilia, lymphopenia, granulocytopenia, lymphocytosis.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of TOPAMAX® has not been evaluated in human studies.

OVERDOSAGE

In acute TOPAMAX® overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has not been shown to adsorb topiramate *in vitro*. Therefore, its use in overdose is not recommended. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdose reported, hemodialysis has not been necessary.

DOSAGE AND ADMINISTRATION

In the controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and clinical efficacy. No evidence of tolerance has been demonstrated in humans. Doses above 400 mg/day (600, 800, and 1000 mg/day) have not been shown to improve responses.

The recommended total daily dose of TOPAMAX® (topiramate capsules) as adjunctive therapy is 400 mg/day in two divided doses. A daily dose of 200 mg/day has inconsistent effects and is less effective than 400 mg/day. It is recommended that therapy be initiated at 50 mg/day followed by titration to an effective dose. Daily doses above 1,600 mg have not been studied.

The recommended titration rate for topiramate is:

	AM DOSE	PM DOSE
Week 1	none	50 mg
Week 2	50 mg	50 mg
Week 3	50 mg	100 mg
Week 4	100 mg	100 mg
Week 5	100 mg	150 mg
Week 6	150 mg	150 mg
Week 7	150 mg	200 mg
Week 8	200 mg	200 mg

It is not necessary to monitor topiramate plasma concentrations to optimize TOPAMAX® therapy. On occasion, the addition of TOPAMAX® to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX® may require adjustment of the dose of TOPAMAX®.

Table 5: Incidence (%) of Dose-Related Adverse Events From Five Placebo-Controlled, Add-On Trials

Adverse Event	TOPAMAX® Dosage (mg/day)		
	Placebo (N=174)	200 (N=45)	400 (N=68)
Fatigue	14.4	11.1	11.8
Nervousness	7.5	13.3	17.6
Difficulty with Concentration/Attention	1.1	6.7	8.8
Confusion	5.2	8.9	10.3
Depression	6.3	8.9	7.4
Anorexia	4.0	4.4	5.9
Language problems	0.6	2.2	8.8
Anxiety	5.2	2.2	2.9
Mood problems	1.7	0.0	5.9
Cognitive problems NOS	0.6	0.0	0.0
Weight decrease	2.3	4.4	8.8
Tremor	6.3	13.3	8.8

small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

Patients with Renal Impairment:

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m²), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

Patients Undergoing Hemodialysis:

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall, below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

Patients with Hepatic Disease:

In hepatically impaired patients topiramate plasma concentrations may be increased. The mechanism is not well understood.

HOW SUPPLIED

TOPAMAX® (topiramate capsules) Sprinkle Capsules contain small, white to off-white spheres. The gelatin capsules are white and clear.

They are marked as follows:

15 mg capsules with "TOP" and "15 mg" on the side.

25 mg capsules with "TOP" and "25 mg" on the side.

The capsules are supplied as follows:

15 mg capsules bottles of 60 (NDC 0045-0647-65)

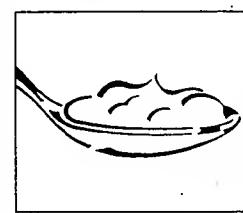
25 mg capsules bottles of 60 (NDC 0045-0645-65)

TOPAMAX® (topiramate capsules) Sprinkle Capsules should be stored in tightly-closed containers at or below 25°C (77°F). Protect from moisture.

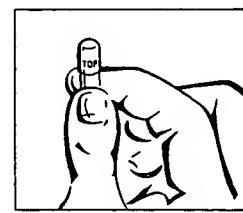
TOPAMAX® (topiramate capsules) is a trademark of OMP DIVISION, ORTHO-MCNEIL PHARMACEUTICAL, INC.

HOW TO TAKE TOPAMAX® (topiramate capsules)**SPRINKLE CAPSULES****A Guide for Patients and Their Caregivers**

Your doctor has given you a prescription for **TOPAMAX®** (topiramate capsules) Sprinkle Capsules. Here are your instructions for taking this medication. Please read these instructions prior to use.

**To Take With Food**

You may sprinkle the contents of **TOPAMAX®** Sprinkle Capsules on a small amount (teaspoon) of soft food, such as applesauce, custard, ice cream, oatmeal, pudding, or yogurt.

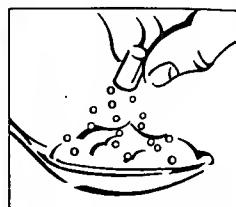


Hold the capsule upright so that you can read the word "TOP".

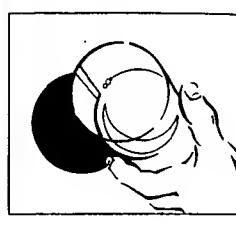


Carefully twist off the clear portion of the capsule. You may find it best to do this over the small portion of the food onto which you will be pouring the

Sprinkle all of the capsule's contents onto a spoonful of soft food, taking care to cover the entire capsule dosage in a small amount of food.



Be sure to swallow the spoonful of the capsule's contents. Do not chew the capsule. It is important to take the capsules whole.



For more information about **TOPAMAX®** Sprinkle Capsules, ask your doctor or pharmacist.

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Raritan, NJ 08869

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Shown in Product Identification Guide, page 22

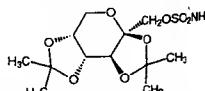
TOPAMAX®

[topiramate] (topiramate) tablets

DESCRIPTION

TOPAMAX® (topiramate) is a sulfamate-substituted saccharide that is intended for use as an antiepileptic drug. It is available as 25 mg, 100 mg, and 200 mg round tablets for oral administration.

Topiramate is a white crystalline powder with a melting point of 170°C. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 1.7 mg/mL. Its saturated solution has a pH of 6.3. The molecular formula is C₁₂H₂₂NO₅S and the molecular weight is 339.36. Topiramate is designated chemically as bis-O-(1-methylethylidene)-β-D-fructopyranose sulfonate and has the following structural formula:



TOPAMAX® (topiramate) Tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hypromellose, methylcellulose, titanium dioxide, polyethylene, synthetic iron oxide (100 and 200 mg tablets) and sorbic acid.

CLINICAL PHARMACOLOGY**Mechanism of Action:**

The precise mechanism by which topiramate exerts its seizure effect is unknown; however, electrophysiological and biochemical studies of the effects of topiramate on cultured neurons have revealed three properties that may contribute to topiramate's antiepileptic efficacy. First, topiramate may reduce the frequency and/or amplitude of repetitive neuronal firing. Second, topiramate may reduce the frequency and/or amplitude of repetitive neuronal firing. Third, topiramate may reduce the frequency and/or amplitude of repetitive neuronal firing.

enhances the ability of GABA to induce a flux into neurons, suggesting that topiramate's activity of this inhibitory neurotransmitter is not blocked by flumazenil; a benzodiazepine. Topiramate increases the duration of the time differentiating topiramate from barbiturates' GABA_A receptors. Third, topiramate has the ability of kainate to activate the kainate/2-hydroxy-5-methyl-isoxazole-4-propionic (AMPA) subtype of excitatory amino acid (glutamate), but has no apparent effect on the activity of NMDA at the NMDA receptor subtypes. The effects of topiramate are concentration-dependent, in the range of 1 μM to 200 μM. Topiramate inhibits some isoenzymes of carbonic anhydrase (CA-IV). This pharmacologic effect is greater than that of acetazolamide, a known carbonic anhydrase inhibitor and is not thought to be a major contributor to topiramate's antiepileptic activity.

Topiramate has anticonvulsant activity in rat and mouse

hot-chuck-seizure (MES) tests. Topiramate is

effective in blocking clonic seizures induced by

receptor antagonist, pentylenetetrazole. Topira-

mate is effective in rodent models of epilepsy, which in-

clude absence-like seizures in the spontaneous ep-

ilepsy (SE) and tonic and clonic seizures induced in

swelling of the amygdala or by global ischemia.

Topiramate is rapid, with peak plasma concen-

trating at approximately 2 hours following a 400

mg oral dose. The relative bioavailability of topiramate from combination is about 80% compared to a solution. Absorption of topiramate is not affected by food.

Pharmacokinetics of topiramate are linear with dose

increases in plasma concentration over the

range (200 to 800 mg/day). The mean plasma

half-life is 21 hours after single or multiple

oral doses. It is thus absorbed in about 4 days in pa-

tient renal function. Topiramate is 13-17%

bound to human plasma proteins over the concentration

range of 250 μg/ml.

Topiramate is excreted:

It is not extensively metabolized and is primarily

excreted in the urine (approximately 70% of

the dose). Six metabolites have been identified

none of which constitutes more than 5% of an

oral dose. The metabolites are formed via hydroxy-

lization and glucuronidation. There is evidence

of tubular reabsorption of topiramate. In rats, given

topiramate, tubular reabsorption, along with topi-

ramate increase in renal clearance of topi-

ramate. This interaction has not been evaluated

Overall, plasma clearance is approximately 20

ml/min in humans following oral administration.

Drug Interactions (see also Drug Interactions):

Interactions between topiramate and standard

concomitant AEDs have been assessed in controlled clinical pharmacokinetic

studies with epilepsy. The effect of these inter-

actions on plasma AUCs are summarized under PRE-

SCRIPTIONS:

Topiramate was reduced by 42% in moderate

creatinine clearance (30-69 ml/min/1.73 m²)

versus severely renally impaired subjects

(creatinine clearance <30 ml/min/1.73 m²) compared to normal

subjects (creatinine clearance >70 mL/min).

Since topiramate is presumed to undergo sig-

nificant reabsorption, it is uncertain whether this

can be generalized to all situations of renal im-

pairment. It is conceivable that some forms of renal disease

can significantly affect glomerular filtration rate and tub-

ular resulting in a clearance of topiramate not

creatinine clearance. In general, however, use

of a low dose is recommended in patients with

moderate renal impairment.

Topiramate was cleared by hemodialysis. Using a high effi-

ciency single pass-dialysis hemodialysis pro-

cedure, a dialysis clearance was 120 mL/min with

through the dialyzer at 400 mL/min. This high

clearance (20-30 mL/min total oral clearance)

will remove a clinically significant

amount of the drug from the patient over the hemodialy-

sis period. Therefore, a dose adjustment may be

required.

SAGE AND ADMINISTRATION:

In paired subjects, the clearance of topira-

mate and the mechanism underlying the de-

creased clearance by hemodialysis was not

affected by age (18-67

years).

Topiramate was evaluated in patients

receiving one or two other antiepileptic

agents. Antiepileptic profiles were obtained after one

and 9 mg/kg/day. Clearance was inde-

Table 1: Topiramate Dose Summary During the Stabilization Periods of Each of Five Double-Blind, Placebo-Controlled, Add-On Trials.

Protocol	Stabilization Dose	Placebo ^a	Target Topiramate Dosage (mg/day)				
			200	400	600	800	1,000
YD	N	42	42	40	41	41	41
	Mean Dose	5.9	200	390	656	656	656
	Median Dose	6.0	200	400	600	800	1,000
YE	N	44	44	40	45	40	40
	Mean Dose	9.7	44	644	739	796	796
	Median Dose	10.0	600	800	1,000	1,000	1,000
Y1	N	23	19	23	23	23	23
	Mean Dose	3.8	395	395	395	395	395
	Median Dose	4.0	400	400	400	400	400
Y2	N	30	28	522	522	522	522
	Mean Dose	5.7	600	600	600	600	600
	Median Dose	6.0	600	600	600	600	600
Y3	N	28	25	568	568	568	568
	Mean Dose	7.9	600	600	600	600	600
	Median Dose	8.0	600	600	600	600	600

^aPlacebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol Y1, 4 tablets/day; Protocols YD and Y2, 6 tablets/day; Protocol Y3, 8 tablets/day; Protocols YE, 10 tablets/day.

Table 2: Median Percent Seizure Rate Reduction and Percent Responders in Five Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Efficacy Results	Placebo	Target Topiramate Dosage (mg/day)				
			200	400	600	800	1,000
YD	N	45	45	45	46	46	46
	Median % Reduction	11.6	27.2 ^b	47.5 ^b	44.7 ^b	44.7 ^b	44.7 ^b
	% Responders	18	24	44	46	47	47
YE	N	47	47	48	48	48	47
	Median % Reduction	1.7	40.8 ^b	41.0 ^b	36.0 ^b	36.0 ^b	36.0 ^b
	% Responders	9	40 ^c	41 ^c	41 ^c	41 ^c	41 ^c
Y1	N	24	23	40.7 ^b	35 ^b	35 ^b	35 ^b
	Median % Reduction	11	35	47.1 ^b	47.1 ^b	47.1 ^b	47.1 ^b
	% Responders	8	30	46.4 ^b	46.4 ^b	46.4 ^b	46.4 ^b
Y2	N	30	12.2	28	24.3 ^b	24.3 ^b	24.3 ^b
	Median % Reduction	10	12.2	28	24.3 ^b	24.3 ^b	24.3 ^b
	% Responders	10	20.6	24.3 ^b	24.3 ^b	24.3 ^b	24.3 ^b
Y3	N	28	20.6	20.6	20.6	20.6	20.6
	Median % Reduction	10	20.6	20.6	20.6	20.6	20.6
	% Responders	10	20.6	20.6	20.6	20.6	20.6

^aComparisons with placebo: ^bp = 0.080, ^cp ≤ 0.010; ^dp ≤ 0.001.

CLINICAL STUDIES

The effectiveness of topiramate as an adjunctive treatment for partial onset seizures was established in five multicenter, randomized, double-blind, placebo-controlled trials, two comparing several dosages of topiramate and placebo, and three comparing a single dosage with placebo, in patients with a history of partial onset seizures, with or without secondarily generalization.

Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® or placebo. In each study, patients were stabilized on optimum dosages of their concomitant AEDs during an 8-12 week baseline phase. Patients who experienced at least 12 (or 8, for 8-week baseline studies) partial onset seizures, with or without secondarily generalization, during the baseline phase were randomly assigned to placebo or a specified dose of TOPAMAX® in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. After titration, patients entered an 8 or 12-week stabilization period. The numbers of patients randomized to each dose, and the actual mean, and median doses in the stabilization period are shown in Table 1.

[See table 1 above]

In all add-on trials, the reduction in seizure rates from baseline during the entire double-blind phase was measured. Responder rate (fraction of patients with at least a 50% reduction) was also measured. The median percent reductions in seizure rates and the responder rates by treatment group for each study are shown in Table 2.

[See table 2 above]

Subset analyses of the antiepileptic efficacy of TOPAMAX® in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

INDICATIONS AND USAGE

TOPAMAX® (topiramate) is indicated as adjunctive therapy for the treatment of adults with partial onset seizures.

CONTRAINDICATIONS

TOPAMAX® (topiramate) is contraindicated in patients with a history of hypersensitivity to any component of this product.

PRECAUTIONS

General

Kidney Stones

A total of 322,086 (1.5%) of patients exposed to topiramate during its development reported the occurrence of kidney stones, an incidence about 2-4 times that expected in a sim-

Topamax—Cont.

An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a weak carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of TOPAMAX® with other carbonic anhydrase inhibitors may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided. Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

Paresthesia

Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®.

Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required (see DOSAGE AND ADMINISTRATION).

Decreased Hepatic Function

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.

Information for Patients:

Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation [see PRECAUTIONS: General, for support regarding hydration as a preventative measure].

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

Drug Interactions:**Antiepileptic Drugs**

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized in the following table:

In Table 3, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added.

The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX® was given alone.

Table 3: Summary of AED Interactions with TOPAMAX®

AED	AED Co-administered	Topiramate Concentration
Phenytoin		NC or 25% increase ^a
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide ^b	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE

^a = Plasma concentration increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin.

^b = is not administered but is an active metabolite of carbamazepine.

NC = Less than 10% change in plasma concentration.

AED = Antiepileptic drug.

NE = Not Evaluated.

Other Drug Interactions

Digoxin: In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established.

CNS Depressants: Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In an interaction study with oral contraceptives using a combination product containing norethindrone and ethynodiol, TOPAMAX® did not significantly affect the clearance of norethindrone. The mean total exposure to the estrogenic component decreased by 18%, 21%, and 30% at daily doses of 200, 400, and 800 mg/day, respectively. Therefore, efficacy of oral contraceptives may be compromised by topiramate. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns. The effect of oral contraceptives on the pharmacokinetics of topiramate is not known.

Others: Concomitant use of TOPAMAX®, a weak carbonic

Table 4: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials^{a,b} (Events occurred in at least 1% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients)

Body System/ Adverse Event ^c	TOPAMAX® Dosage (mg/day)		
	Placebo (N=174)	200-400 (N=113)	600-1,000 (N=241)
Body as a Whole - General Disorders			
Asthenia	1.1	8.0	4.5
Back Pain	4.0	6.2	2.0
Chest Pain	2.3	4.4	2.0
Influenza-Like Symptoms	2.9	3.5	2.0
Leg Pain	2.3	3.5	3.2
Hot Flushes	1.7	2.7	2.4
Body Odor	0.0	1.8	0.8
Edema	1.1	1.8	0.0
Rigors	0.0	1.8	1.2
Central & Peripheral Nervous System Disorders			
Dizziness	14.4	28.3	32.4
Ataxia	6.9	21.2	17.0
Speech Disorders/ Related Speech Problems	2.9	16.8	13.8
Nystagmus	11.5	15.0	15.0
Paresthesia	3.4	15.0	14.8
Tremor	6.3	10.6	13.8
Language Problems	0.6	6.2	11.7
Coordination Abnormal	1.7	5.3	3.6
Hypoesthesia	1.1	2.7	0.8
Gastrointestinal System Disorders			
Nausea	6.3	11.5	13.8
Dyspepsia	5.2	8.0	5.7
Abdominal Pain	2.9	5.3	7.3
Constipation	0.6	5.3	3.2
Dry Mouth	1.1	2.7	3.2
Gingivitis	0.0	1.8	0.4
Hearing and Vestibular Disorders			
Hearing Decreased	1.1	1.8	1.6
Metabolic and Nutritional Disorders			
Weight Decrease	2.3	7.1	12.6
Musculoskeletal System Disorders			
Myalgia	1.1	1.8	1.2
Platelet, Bleeding and Clotting Disorders			
Epistaxis	1.1	1.8	0.8
Psychiatric Disorders			
Somnolence	10.3	30.1	25.9
Psychomotor Slowing	2.3	16.8	25.1
Nervousness	7.5	15.9	20.6
Difficulty with Memory	2.9	12.4	12.6
Confusion	5.2	9.7	15.0
Depression	6.3	8.0	13.4
Difficulty with Concentration/Attention	1.1	8.0	15.4
Anorexia	4.0	5.3	11.3
Agitation	1.7	4.4	4.0
Mood Problems	1.7	3.5	10.1
Aggressive Reaction	0.6	2.7	4.0
Apathy	0.0	1.8	4.5
Depersonalization	0.6	1.8	1.6
Emotional Lability	1.1	1.8	2.4
Reproductive Disorders, Female			
Breast Pain, Female	0.0	8.3	0.0
Dysmenorrhea	2.6	8.3	0.0
Menstrual Disorder	0.0	4.2	0.0
Respiratory System Disorders			
Upper Respiratory Infection	11.5	12.4	12.1
Pharyngitis	2.9	7.1	2.3
Sinusitis	4.0	4.4	4.0
Dyspnea	1.1	1.8	3.2
Skin and Appendages Disorders			
Rash	4.0	4.4	3.2
Pruritus	1.1	1.8	3.2
Sweating Increased	0.0	1.8	0.4
Urinary System Disorders			
Hematuria	0.6	1.8	0.8
Vision Disorders			
Diplopia	6.3	14.2	14.6
Vision Abnormal	2.9	14.2	10.3
Eye Pain	1.1	1.8	2.0
White Cell and Res Disorders			
Leukopenia	0.6	2.7	1.6

^a Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX or placebo.

^b Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

^c Adverse events reported by at least 1% of patients in the TOPAMAX 200-400 mg/day group and more common than placebo group are listed in this table.

Laboratory Tests: There are no known interactions of topiramate with commonly used laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was measured in patients receiving topiramate therapy at the recommended human dose (RHD) of 400 mg/day and 1.5 to 2 times steady state topiramate exposure in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in mice following oral administration of topiramate for 2 years.

Table 5: Incidence (%) of Dose-Related Adverse Events From Five Placebo-Controlled, Add-On Trials

Adverse Event	TOPAMAX® Dosage (mg/day)			
	Placebo (N=174)	200 (N=45)	400 (N=68)	600-1,000 (N=247)
Fatigue	14.4	11.1	11.8	30.8
Nervousness	7.5	13.3	17.6	20.6
Difficulty with Concentration/Attention	1.1	6.7	8.8	15.4
Confusion	5.2	8.9	10.3	15.0
Depression	6.3	8.9	7.4	13.4
Anorexia	4.0	4.4	5.9	11.3
Language problems	0.6	2.2	8.8	11.7
Anxiety	5.2	2.2	2.9	9.3
Mood problems	1.7	0.0	5.9	10.1
Cognitive problems NOS	0.6	0.0	0.0	4.0
Weight decrease	2.3	4.4	8.8	12.6
Tremor	6.3	13.3	8.8	13.8

guage problems, anxiety, mood problems, cognitive problems not otherwise specified, weight decreased, and tremor (see Table 5).

In controlled clinical trials, 11% of patients receiving topiramate 200 to 400 mg/day as adjunctive therapy discontinued due to adverse events. This rate appeared to increase at dosages above 400 mg/day. Adverse events associated with discontinuing therapy included somnolence, dizziness, anxiety, difficulty with concentration or attention, fatigue, and paresthesia and increased at dosages above 400 mg/day. Approximately 28% of the 1,715 individuals with epilepsy who received topiramate at dosages of 200 to 1,600 mg/day in clinical studies discontinued treatment because of adverse events; an individual patient could have reported more than one adverse event. These adverse events were: psychomotor slowing (4.1%), difficulty with memory (3.3%), fatigue (3.3%), confusion (3.2%), somnolence (3.2%), difficulty with concentration/attention (2.9%), anorexia (2.9%), depression (2.6%), dizziness (2.6%), weight decrease (2.5%), nervousness (2.2%), ataxia (2.2%), paresthesia (2.0%), and language problems (2.0%).

Incidence in Controlled Clinical Trials - Add-On Therapy
Table 4 lists treatment-emergent adverse events that occurred in at least 1% of patients treated with 200 to 400 mg/day topiramate in controlled trials that were numerically more common at this dose than in the patients treated with placebo. In general, most patients who experienced adverse events during the first eight weeks of these trials no longer experienced them by their last visit.

The prescriber should be aware that these data were obtained when TOPAMAX® was added to concurrent antiepileptic drug therapy and cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with data obtained from other clinical investigations involving different treatments, uses, or investigators. Inspection of these frequencies, however, does not provide the prescribing physician with a basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

[See table 4 at top of previous page]
[See table 5 above]

Other Adverse Events Observed

Other events that occurred in more than 1% of patients treated with 200 to 400 mg of topiramate in placebo-controlled trials but with equal or greater frequency in the placebo group were: fatigue, headache, injury, anxiety, rash, pain, convulsions aggravated, coughing, gastroenteritis, rhinitis, back pain, hot flushes, bronchitis, abnormal gait, involuntary muscle contractions, and epistaxis.

Other Adverse Events Observed During All Clinical Trials

Topiramate, initiated as adjunctive therapy, has been administered to 1,715 patients with epilepsy during all clinical studies. During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. The frequencies presented represent the proportion of 1,715 topiramate-treated patients who experienced an event of the type cited on at least one occasion while receiving topiramate. Reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* occurring in at least 1/100 patients; *infrequent* occurring in 1/100 to 1/1000 patients; *rare* occurring in fewer than 1/1000 patients.

Autonomic Nervous System Disorders: *Infrequent:* vasodilation.

Body as a Whole: *Frequent:* fatigue, fever, malaise. *Infrequent:* syncope, halitosis, abdomen enlarged. *Rare:* alcohol intolerance, substernal chest pain, sudden death.

Cardiovascular Disorders, General: *Infrequent:* hypertension, hypotension, postural hypotension.

Central & Peripheral Nervous System Disorders: *Frequent:* hypokinesia, vertigo, stupor, convulsions grand mal, hypokinesia, hypertension. *Infrequent:* leg cramps, hyporeflexia, neuropathy, migraine, encephalopathy, headache, dizziness.

field defect, coma, encephalopathy, fecal incontinence, upper motor neuron lesion. *Rare:* cerebellar syndrome, EEG abnormal, tongue paralysis.

Endocrine Disorders: *Infrequent:* goiter. *Rare:* thyroid disorder.

Gastrointestinal System Disorders: *Frequent:* diarrhea, vomiting, flatulence, gastroenteritis. *Infrequent:* gum hyperplasia, hemorrhoids, tooth caries, stomatitis, dysphagia, melena, gastritis, saliva increased, hiccup, gastroesophageal reflux, tongue edema, esophagitis. *Rare:* eructation.

Haaring and Vestibular Disorders: *Frequent:* tinnitus. *Rare:* earache, hyperacusis.

Heart Rate and Rhythm Disorders: *Frequent:* palpitation. *Infrequent:* AV block bradycardia, bundle branch block. *Rare:* arrhythmia, arrhythmia atrial, fibrillation atrial.

Liver and Biliary System Disorders: *Infrequent:* SGPT increased, SGOT increased, gall bladder disorder. *Rare:* gamma-GT increased.

Metabolic and Nutritional Disorders: *Frequent:* weight increase. *Infrequent:* thirst, hypokalemia, alkaline phosphatase increased, dehydration, hypocalcemia, hyperlipemia, acidosis, hyperglycemia, creatinine increased, hyperchloraemia, xerophthalmia. *Rare:* diabetes mellitus, hypernatremia, abnormal serum folate, hyponatremia, hypcholesterolemia, hypoglycemia, hypophosphatemia.

Musculoskeletal System Disorders: *Frequent:* arthralgia, muscle weakness. *Infrequent:* arthrosis, osteoporosis.

Myo-, Endo-, Pericardial & Valve Disorders: *Infrequent:* angina pectoris.

Neoplasms: *Infrequent:* basal cell carcinoma, thrombocytopenia. *Rare:* polycythemia.

Platelet, Bleeding, and Clotting Disorders: *Infrequent:* gingival bleeding, purpura; thrombocytopenia, pulmonary embolism.

Psychiatric Disorders: *Frequent:* insomnia, personality disorder, impotence, hallucination, euphoria, psychosis, libido decreased, suicide attempt. *Infrequent:* paranoid reaction, appetite increased, delusion, paranoia, delirium, abnormal dreaming, neurosis. *Rare:* libido increased, manic reaction.

Red Blood Cell Disorders: *Frequent:* anemia. *Rare:* marrow depression, pancytopenia.

Reproductive Disorders, Female: *Frequent:* intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis, amenorrhea.

Reproductive Disorders, Male: *Infrequent:* ejaculation disorder, breast discharge.

Respiratory System Disorders: *Frequent:* coughing, bronchitis. *Infrequent:* asthma, bronchospasm. *Rare:* laryngismus.

Skin and Appendages Disorders: *Frequent:* acne, alopecia. *Infrequent:* dermatitis, nail disorder, folliculitis, dry skin, urticaria, skin discoloration, eczema, photosensitivity reaction, erythematous rash, seborrhea, sweating decreased, abnormal hair texture. *Rare:* chloasma.

Special Senses Other Disorders: *Frequent:* taste perversion. *Infrequent:* taste loss, parosmia.

Urinary System Disorders: *Frequent:* urinary tract infection, micturition frequency, urinary incontinence, dysuria, renal calculus. *Infrequent:* urinary retention, face edema, renal pain, nocturia, albuminuria, polyuria, oliguria.

Vascular (Extracardiac) Disorders: *Infrequent:* flushing, deep vein thrombosis, phlebitis. *Rare:* vasospasm.

Vision Disorders: *Frequent:* conjunctivitis. *Infrequent:* abnormal accommodation, photophobia, abnormal lacrimation, strabismus, color blindness, myopia, mydriasis. *Rare:* cataract, corneal opacity, iritis.

White Cell and Reticulendothelial System Disorders: *Infrequent:* lymphadenopathy, eosinophilia, lymphopenia, granulocytopenia, lymphocytosis.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of TOPAMAX® (topiramate) has not been evaluated in human studies.

OVERDOSAGE

In acute TOPAMAX® (topiramate) overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has not been shown to adsorb topiramate *in vitro*. Therefore, its use in overdosage is not recommended. Treatment should be ap-

Topamax—Cont.

propriately supportive. Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdosage reported, hemodialysis has not been necessary.

DOSAGE AND ADMINISTRATION

In the controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and clinical efficacy. No evidence of tolerance has been demonstrated in humans. Doses above 400 mg/day (600, 800, and 1000 mg/day) have not been shown to improve responses.

The recommended total daily dose of TOPAMAX® (topiramate) as adjunctive therapy is 400 mg/day in two divided doses. A daily dose of 200 mg/day has inconsistent effects and is less effective than 400 mg/day. It is recommended that therapy be initiated at 50 mg/day followed by titration to an effective dose. Daily doses above 1,600 mg have not been studied.

The recommended titration rate for topiramate is:

	AM DOSE	PM DOSE
Week 1	none	50 mg
Week 2	50 mg	50 mg
Week 3	50 mg	100 mg
Week 4	100 mg	100 mg
Week 5	100 mg	150 mg
Week 6	150 mg	150 mg
Week 7	150 mg	200 mg
Week 8	200 mg	200 mg

It is not necessary to monitor topiramate plasma concentrations to optimize TOPAMAX® therapy. On occasion, the addition of TOPAMAX® to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX® may require adjustment of the dose of TOPAMAX®. Because of the bitter taste, tablets should not be broken. TOPAMAX® can be taken without regard to meals.

Patients with Renal Impairment:

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m²), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

Patients Undergoing Hemodialysis:

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

Patients with Hepatic Disease:

In hepatically impaired patients topiramate plasma concentrations may be increased. The mechanism is not well understood.

HOW SUPPLIED

TOPAMAX® (topiramate) is available as debossed, coated, round tablets in the following strengths and colors: 25 mg white (coded "TOP" on one side; "25" on the other) 100 mg yellow (coded "TOPAMAX" on one side; "100" on the other)

200 mg salmon (coded "TOPAMAX" on one side; "200" on the other)

They are supplied as follows:

25 mg tablets - bottles of 60 count with desiccant (NDC 0045-0639-65)

100 mg tablets - bottles of 60 count with desiccant (NDC 0045-0641-65)

200 mg tablets - bottles of 60 count with desiccant (NDC 0045-0642-65)

TOPAMAX® (topiramate) Tablets should be stored in tightly-closed containers at controlled room temperature, (59 to 86°F, 15 to 30°C). Protect from moisture.

TOPAMAX® (topiramate) is a trademark of OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC.

Raritan, NJ 08869

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Shown in Product Identification Guide, page 329

TYLENOL® with Codeine

[ti'len-awl co'den]

(acetaminophen and codeine phosphate tablets and oral solution USP)

Tablets and Elixir

Analgesic For Oral Use

No. 3-NSN 6505-00-400-2054—100's

No. 3-NSN 6505-00-147-8347—500's

No. 3-NSN 6505-01-086-2993—U/D 500's

No. 3-NSN 6505-00-372-3032—1000's

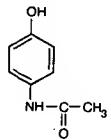
Elixir-NSN 6505-01-035-1963—Pints

No. 3 Codeine Phosphate*	30 mg
Acetaminophen	300 mg
No. 4 Codeine Phosphate*	60 mg
Acetaminophen	300 mg
Each 5 mL of elixir contains:	
Codeine Phosphate*	12 mg
Acetaminophen	120 mg
Alcohol	7%

*Warning—May be habit forming.

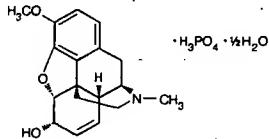
Inactive ingredients: tablets—powdered cellulose, magnesium stearate, sodium metabisulfite†, pregelatinized starch, starch (corn); elixir—alcohol, citric acid, propylene glycol, sodium benzoate, saccharin sodium, sucrose, natural and artificial flavors, FD&C Yellow No.6.

Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. Its structure is as follows:



C₈H₉NO M.W. 151.16

Codeine is an alkaloid, obtained from opium or prepared from morphine by methylation. Codeine phosphate occurs as fine, white, needle-shaped crystals, or white, crystalline powder. It is affected by light. Its chemical name is: 7,8-dihydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate. Its structure is as follows:



C₁₈H₂₁NO₃H₃PO₄·½H₂O M.W. 406.37

†See WARNINGS

CLINICAL PHARMACOLOGY

TYLENOL with Codeine (acetaminophen and codeine phosphate tablets and oral solution USP) combine the analgesic effects of a centrally acting analgesic, codeine, with a peripherally acting analgesic, acetaminophen. Both ingredients are well absorbed orally. The plasma elimination half-life ranges from 1 to 4 hours for acetaminophen, and from 2.5 to 3 hours for codeine.

Codeine retains at least one-half of its analgesic activity when administered orally. A reduced first-pass metabolism of codeine by the liver accounts for the greater oral efficacy of codeine when compared to most other morphine-like narcotics. Following absorption, codeine is metabolized by the liver and metabolic products are excreted in the urine. Approximately 10 percent of the administered codeine is demethylated to morphine, which may account for its analgesic activity.

Acetaminophen is distributed throughout most fluids of the body, and is metabolized primarily in the liver. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

INDICATIONS AND USAGE

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) are indicated for the relief of mild to moderately severe pain.

TYLENOL with Codeine elixir (acetaminophen and codeine phosphate oral solution USP) is indicated for the relief of mild to moderate pain.

CONTRAINDICATIONS

TYLENOL with Codeine tablets or elixir (acetaminophen and codeine phosphate tablets and oral solution USP) should not be administered to patients who have previously exhibited hypersensitivity to any component.

WARNINGS

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS**General**

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exag-

Acute Abdominal Conditions: The administration of product or other narcotics may obscure the diagnosis of acute abdominal conditions.

Special Risk Patients: This drug should be given with caution to certain patients such as the elderly, debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Information for Patients

Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient should understand the single-dose and total dose limits, and the time interval between doses.

Drug Interactions

Patients receiving other narcotic analgesics, antihistamines, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with this drug may exhibit additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced. The concurrent use of anticholinergics with codeine may produce paralytic ileus.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed with acetaminophen or codeine to determine carcinogenic potential or effects on fertility.

Acetaminophen and codeine have been found to have mutagenic potential using the Ames Salmonella Microsome Activation test, the Basc test on Drosophila melanogaster, and the Micronucleus test on mouse bone marrow cells.

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Codeine: A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the animal, were associated with an increase in embryotoxicity at the time of implantation. In another study, a 100 mg/kg dose of codeine administered to pregnant rats reportedly resulted in delayed ossification in the offspring. There are no studies in humans, and the significance of these findings to humans, if any, is not known.

TYLENOL with Codeine (acetaminophen and codeine phosphate tablets and oral solution USP) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:

Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Withdrawal signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. These signs usually appear during the first few days of life.

Labor and Delivery

Narcotic analgesics cross the placental barrier. The closer delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see OVERDOSE). The effect of codeine, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

Some studies, but not others, have reported detectable amounts of codeine in breast milk. The levels are probably not clinically significant after usual therapeutic doses. The possibility of clinically important amounts being excreted in breast milk in individuals abusing codeine should be considered.

Pediatric Use

Safe dosage of TYLENOL with Codeine elixir (acetaminophen and codeine phosphate oral solution USP) has not been established in children below the age of three years.

ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, shortness of breath, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include allergic reactions, euphoria, dysphoria, constipation, abdominal pain, and pruritus.

At higher doses, codeine has most of the disadvantages of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) are a Schedule III controlled substance.

TYLENOL with Codeine elixir (acetaminophen and codeine phosphate oral solution USP) is a Schedule V controlled substance.

Codeine can produce drug dependence of the morphine type, and, therefore, has the potential for being abused. Psycho-



DECLARATION UNDER 37 C.F.R. § 1.132
Examining Group 1614
Patent Application
Docket No. UF-260XC1
Serial No. 09/997,447

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Phyllis G. Spivack
Art Unit : 1614
Applicants : Nathan Andrew Shapira, Mary Catherine Lessig, Daniel John Driscoll
Serial No. : 09/997,447
Filed : November 30, 2001
Conf. No. : 3440
For : Treatments for Neurogenetic Disorders, Impulse Control Disorders, and
Wound Healing

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

DECLARATION OF DAVID W. MOZINGO, M.D., UNDER 37 C.F.R. §1.132

Sir:

I, David W. Mozingo, M.D., hereby declare:

THAT, I have received the following degrees:

Doctor of Medicine 1984 University of Virginia School of Medicine,
Charlottesville, Virginia

Bachelor of Science 1980 University of Virginia, Charlottesville, Virginia
in Chemistry

THAT, I have been employed professionally as follows:

Postdoctoral Training

1990- 1991 Fellowship, Surgical Critical Care Fellowship, Brooke Army Medical Center, Fort Sam Houston, Texas

1986-1990 Residency, General Surgery Residency, Brooke Army Medical Center, Fort Sam Houston, Texas

1984-1985 Internship, Categorical Surgery Internship, Brooke Army Medical Center, Fort Sam Houston, Texas

Academic Appointments

2002-present Professor of Surgery and Anesthesiology, University of Florida College of Medicine, Gainesville, Florida

1996 – 2002 Associate Professor of Surgery and Anesthesiology, University of Florida College of Medicine, Gainesville, Florida

1992 – 1996 Clinical Assistant Professor of Surgery, University of Texas Health Science Center, San Antonio, Texas

1993 – 1996 Assistant Professor of Surgery, F. Edward Hebert School of Medicine, Uniformed Services University of Health Science, Bethesda, Maryland

1992 – 1992 Clinical Instructor in Surgery, University of Texas Health Science Center, San Antonio, Texas

1991 – 1996 Faculty, Surgical Critical Care Fellowship, Brooke Army Medical Center, Fort Sam Houston, Texas

1991 – 1996 Faculty, General Surgery Residency Program, Brooke Army Medical Center, Fort Sam Houston, Texas

1990 – 1993 Instructor of Surgery, F. Edward Hebert School of Medicine, Uniformed Services University of Health Science, Bethesda, Maryland

THAT, I have authored approximately sixty research papers, chapters and review articles publications (a sampling of which is included on the attached Curriculum Vitae);

THAT, through my years of research, I have kept up to date on the technical literature and maintained contact with experts in the field by participating in professional meetings and

seminars, and by direct personal contact. As a result, I am familiar with the general level of skill of those working in the field of wound healing;

THAT, I have studied application Serial No. 09/997,447, filed on November 30, 2001, the Office Actions which have been issued during prosecution of this application, the references cited in these Office Actions, and the responses which have been filed on the behalf of Applicants. Thus, being duly qualified, I declare as follows:

1. I have reviewed the disclosure of Blake *et al.* (International Application PCT /GB99/02606; International Publication No. WO 00/10610) and cannot agree with the assertion of the Patent Office that this reference would motivate one skilled in the art to use topiramate to promote wound healing. The reference is directed to the manufacture and use of bioreductive conjugates for the treatment of a variety of conditions or diseases. While the reference addresses or claims medicaments for "use in the healing of wounds or the treatment of fibrotic disorders", the therapeutic agents indicated as being useful in this regard are limited to growth factor neutralizing agents or agents specific against only fibrotic growth factors (see claims 2 and 3); the reference specifically speaks to neutralizing growth factors, interleukins, or other agents that are typically associated with inducing fibrosis or scarring. Specific examples of such agents that are provided in the description of Blake *et al.* are TGF- β 1; TGF- β 2; PDGF; IFN γ ; IL-1; TGF- β 3; FGF-1; FGF-2; IL-4; IL-10; betaglycan; inhibitors of: IFN- γ , at least one integrin receptor, at least one convertase enzyme, or IL-6; stimulators of: IFN- γ or activin and/or inhibin; agents that modulate actin assembly and organization, latency associated peptide; insulin like growth factor II; or compounds that influence the sex hormone system (see claims 4-21 and the description of the embodiment directed to wound healing at pages 4-14). Indeed, the description at pages 4-14 repeatedly states that the embodiments discussed on these pages are directed to wound healing (see, for example, page 7, paragraph 5; page 8, paragraphs 1 and 4; page 9, paragraphs 2 and 6; page 10, paragraph 2; page 11, paragraphs 3 and 7; page 12, paragraphs 2 and 5; page 13, paragraph 4; and page 14, paragraphs 1 and 4).

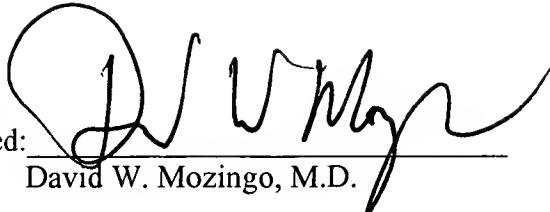
I note that topiramate is absent from the listing of agents for use in promoting the healing of wounds or the treatment of fibrotic disorders. This is not surprising as, to the best of my knowledge, there was no recognition (nor was it suspected) that topiramate had such an activity prior to the filing date of this patent application. As the Patent Office may be aware, topiramate is a drug recommended for the treatment of epilepsy (as is disclosed in the description of Blake *et al.* at page 15, paragraph 1 and the Physician's Desk Reference, a copy of which is appended hereto).

As one skilled in the art, I would not have been motivated to use topiramate for the treatment of wounds or for promoting wound healing in view of the teachings of Blake *et al.* Rather, I would have been motivated to use topiramate for the treatment of epilepsy. Furthermore, as one skilled in the art, I would not, and could not, reasonably infer that the reference teaches or suggests or motivates the use of topiramate for promoting wound healing as is argued by the Patent Office.

2. As indicated above, there was, to the best of my knowledge, no recognition in the art that topiramate was useful for promoting wound healing in individuals to whom topiramate was administered and, based upon my experience in the field, I would not have expected topiramate to provide therapeutic benefit in promoting wound healing.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Signed: 
David W. Mozingo, M.D.

Date: 9/22/04

Attachments: Physician's Desk Reference (2000)

CURRICULUM VITAE

David W. Mozingo, MD, FACS

October 6, 2004

PERSONAL INFORMATION

Citizenship	United States
Business Address	University of Florida Department of Surgery PO Box 100286 Gainesville, FL 32610-0286
Business Telephone	352-265-0262
Business Fax	352-338-9809

EDUCATION

Undergraduate	University of Virginia, Charlottesville, Virginia Bachelor of Science in Chemistry May 1980
Medical School	University of Virginia School of Medicine Charlottesville, Virginia, Doctor of Medicine May 1984

POSTGRADUATE TRAINING

Fellowship	Surgical Critical Care Fellowship, Brooke Army Medical Center, Fort Sam Houston, Texas, July 1990-June 1991
Residency	General Surgery Residency, Brooke Army Medical Center, Fort Sam Houston, Texas, July 1986-June 1990
Internship	Categorical Surgery Internship, Brooke Army Medical Center, Fort Sam Houston, Texas, July 1984-June 1985

AWARDS

American Burn Association Traveling Fellowship, April 1992
General Surgery Resident Research Award, Brooke Army Medical Center, June 1988
University of Virginia – Graduation with Distinction, May 1980
University of Virginia – Intermediate Honors, 1978
Meritorious Service Medal
US Army Superior Unit Award

National Defense Service Medal
Air Crew Member Badge
Army Service Ribbon

PROFESSIONAL LICENSES & BOARD CERTIFICATIONS

1986-Present License – Commonwealth of Virginia #0101040452 10/31/86
1996-Present License – State of Florida #ME0070020 2/26/96

American Board of Surgery, 2/28/91, Re-certification 1999
American Board of Surgery, Certificate of Added Qualifications in Surgical Critical Care, 10/18/91, Re-certification 2000
National Board of Medical Examiners, April 1986
American College of Surgeons – Advance Trauma Life Support – Provider, April 1985
American College of Surgeons – Advanced Trauma Life Support – Instructor, March 1990, Re-certification March 1994
American Heart Association – Advanced Cardiac Life Support – Provider, March 1996
American Burn Association – Advanced Burn Life Support – Instructor/Provider, February 1994; National Faculty, 1995

ACADEMIC APPOINTMENTS

2002 – present Professor of Surgery and Anesthesiology
University of Florida College of Medicine
Gainesville, Florida

1996 – 2002 Associate Professor of Surgery and Anesthesiology
University of Florida College of Medicine
Gainesville, Florida

1992 – 1996 Clinical Assistant Professor of Surgery
University of Texas Health Science Center
San Antonio, Texas

1993 – 1996 Assistant Professor of Surgery
F. Edward Hebert School of Medicine
Uniformed Services University of Health Science
Bethesda, Maryland

1992 – 1992 Clinical Instructor in Surgery
University of Texas Health Science Center
San Antonio, Texas

1991 – 1996 Faculty, Surgical Critical Care Fellowship
Brooke Army Medical Center
Fort Sam Houston, Texas

1991 – 1996 Faculty, General Surgery Residency Program
Brooke Army Medical Center
Fort Sam Houston, Texas

1990 – 1993 Instructor of Surgery
F. Edward Hebert School of medicine
Uniformed Services University of Health Science
Bethesda, Maryland

HOSPITAL APPOINTMENTS

1996-2003 Burn Center Director
Shands Burn Center at the University of Florida
Gainesville, Florida

1995-1996 Chief, Clinical Division
U.S. Army Institute of Surgical Research
Fort Sam Houston, Texas

1994-1995 Chief, Burn Study Branch
U.S. Army Institute of Surgical Research
Fort Sam Houston, Texas

1991-1994 Staff Surgeon
U.S. Army Institute of Surgical Research
Fort Sam Houston, Texas

1985-1986 General Medical Officer
U.S. Army Institute of Surgical Research
Fort Sam Houston, Texas

NATIONAL COMMITTEES

American Burn Association

2003-2004 Interim ABA Region 1V Chairman

2002-present Ad Hoc Committee for Disaster Response Planning

2001-present Organization and Delivery of Burn Care, Chair

2000-present ABLS Advisory Committee

2000-2003 Committee on Government Affairs

1998-2003 Region 1V Chairman, ABA

1998-2003 Regionalization Committee, Region IV Southeast

1994-1996 Regionalization Committee, Region XII Military

1994-2000 Organization and Delivery of Burn Care

American Board of Surgery

2002 Associate Examiner, Jacksonville, Florida

STATE AND LOCAL COMMITTEES

1999-present	Member, Required Criteria for Consultation and Transfer Subcommittee Trauma Program, Bureau of Emergency Medical Services, Florida Department of Health
1999-2004	Team Leader, Southeast Region Burn Specialty Team, National Disaster Medical System
1999-2001	Secretary, Southeast Burn Foundation
1997-1999	Chairman, Southeast Burn Foundation
1995-1996	Southwest Texas Regional Advisory Council
1995-1996	Greater San Antonio Hospital Council Critical Care Transfer Coordinating Board

INSTITUTIONAL COMMITTEES

2002-present	Shands HealthCare ICU Improvement Committee
2001-present	Informed Consent Committee, Shands Hospital, University of Florida College of Medicine
2000-2001	Chairman, Search Committee, Division of General Surgery, Shands Hospital, University of Florida, College of Medicine
1999-present	Chairman, Search Committee, Division of Burn Surgery, Shands Hospital, University of Florida, College of Medicine Faculty
1996-present	Chairman, Burn Center QI Committee Shands Hospital, Gainesville, Florida
1996-present	Infection Control Committee, Shands Hospital, Gainesville, Florida
1996-2000	Pharmacy and Therapeutics Committee Shands Hospital, Gainesville, Florida
1997-2000	Faculty Senate University of Florida, Gainesville, Florida
1997-1997	Level I Trauma Work Group Shands Hospital, Gainesville, Florida
1995-1996	Graduate Medical Education Committee Brooke Army Medical Center, Fort Sam Houston, Texas
1995-1996	Multidisciplinary Trauma Committee Brooke Army Medical Center, Fort Sam Houston, Texas
1994-1996	U.S. Army Institute of Surgical Research Council Fort Sam Houston, Texas
1994-1996	Chairman, Infection Control Committee, U.S. Army Institute of Surgical Research, Fort Sam Houston, Texas
1993-1996	Hospital Credentials Committee, Brooke Army Medical Center, Fort Sam Houston, Texas
1992-1996	Animal Use Committee, U.S. Army Institute of Surgical Research, Fort Sam Houston, Texas
1991-1992	Surgical Quality Assurance Committee, Brooke Army Medical Center, Fort Sam Houston, Texas
1990-1992	Animal Use Committee, Brooke Army Medical Center, Fort Sam Houston, Texas

SOCIETY MEMBERSHIPS

Florida Committee on Trauma, 2002
Alachua County Medical Society, 1996
Florida Surgical Society, 1996
American College of Surgeons, Fellow, 1994
The Society of University Surgeons, 2000
American Association for the Surgery of Trauma, 1995
Association for Academic Surgery, 1992
Surgical Infection Society, 1995
Society of Critical Care Medicine, 1991
Society of American Gastrointestinal Endoscopic Surgeons, 1991
American Burn Association, 1991
International Society for Burn Injuries, 1993
American Trauma Society, 1995
Wound Healing Society, 1999
South Texas Chapter, American College of Surgeons, 1994-1996
San Antonio Surgical Society – 1994-1996
International Association for the Surgery of Trauma and Surgical Intensive Care, 1996
International Association for Surgical Metabolism and Nutrition, 1999
Shock Society
International Society of Surgery – Société Internationale De Chirurgie ISS/SIC, 1996
American Society for Parenteral and Enteral Nutrition, 1999
Eastern Association for the Surgery of Trauma, 1998
Association for the Advancement of Wound Care, 2001
Venezuelan Surgical Society (honorary member), 2000
Argentinian Burn Society (honorary member), 2001
American Board of Surgery Associate Examiner, 2001

VISITING PROFESSORSHIPS

1. Department of Surgery, Temple University, Philadelphia, Pennsylvania, May 14, 2003.
2. Cook County Hospital, Burn Center, Chicago, Illinois, May 18, 2001.
3. Profesore Internationale Invitado, VI Congreso Venezolano de Quemaduras, Ciudad Bolívar, Venezuela, July 24-26, 1997
4. Department of Surgery, University of North Dakota, January 29, 1997
5. Baton Rouge Regional Burn Center, Baton Rouge, Louisiana, September 17, 1992.

EDITORIAL POSITIONS

2002-present Editor, *Yearbook of Surgery*, Section of Burns, Trauma and Critical Care
2000-present Editorial Board, *Journal of Burn Care and Rehabilitation*
1993-present Ad hoc editor, *Journal of Trauma*

FUNDING/SOURCE

Cosmesis and Donor Site Assessment Plus a Thin Split-Thickness Skin Graft

(STSG) Compared to Standard-Thickness STSG Alone in Treatment of Full-Thickness Burn Wounds, LifeCell Corporation, 1998-complete, \$15,000.

A Phase II Randomized, Double Blind, Placebo-Controlled, Multiple-Dose, Parallel Group, Multi-Center Study of the Effects of PB005 on Reepithelialization of Donor Sites in Patients with Burns Which Require Skin Grafting, Pharmadigm, 1998-complete, \$20,728.00.

An Open Label Study to Evaluate the Incidence of Wound Infection in Patients Requiring a Temporary Covering for Excised Burn Wounds, Advanced Tissue Sciences, 1998-complete, \$47,500.00.

T32 Shock/Trauma Training Grant, NIH, 1999-2003, \$306,233, Clinical Mentor, Primary Investigator, Lyle Moldawer, PhD.

A Randomized Feasibility Study to Determine the Appropriate Number and Schedule of Application of a Collagen Matrix Containing Allograft Cells for the Treatment of Venous Ulcers, Ortec International, Inc., 2/3/99 – complete, \$57,500.00.

Controlled Randomized Multi-center Study of the Effects of a Composite Cultured Skin Containing a Collagen Matrix Seeded with Allograft Cells on the Management of Split Thickness Donor Sites in Burn Patients, Ortec International, Inc., 7/21/99-complete, \$38,750.00.

A Multi-center, Matched-Wound, Randomized, Open-Label Study to Compare the Healing Time of Acticoat© Silver-coated Dressing Compared with Xeroform Dressing in the Treatment of Partial-thickness Donor Site Wounds, Westaim Biomedical, Inc., 8/21/99-complete, \$82,968.75.

A Multicenter, Retrospective Chart and Database Review of Patients with Toxic Epidermal Necrolysis Syndrome, 1/1/00-4/8/01.

A Randomized, Controlled, Within-patient-paired Study to Compare the Effectiveness of TransCyte™ and Biobrane© in the Treatment of Mid-Dermal to Indeterminate Depth Burn Wounds, 5/17/00-complete, \$47,500.00.

A Molecular Analysis of Burn and Chronic Wound Healing, 6/1/00-present.

A Multicenter, Retrospective Chart and Database Review of Subjects with Tens/Stevens-Johnson Syndrome, 6/16/00-complete.

Clinical Evaluation of Regranex© (beprotermin) Gel 0.01% for the Treatment of Full Thickness Diabetic Neuropathic Foot Ulcers, 6/19/00-complete, \$75,000.00.

Measurement of Burn Wound Elasticity Using Biomechanical Tissue Characterization, BTC-2000, 7/14/00-complete, \$4,000.00.

Molecular Analysis of Burn and Wound Tissue Collected from Various Patients at Different Stages of Healing, 8/3/00-present.

Pilot Prospective Clinical Assessment of the Impact of Acticoat Silvercoated Antimicrobial Dressings on Cytokines and MMP's in Non-healing Wounds, 9/20/00 –complete, \$50,440.00.

A Multicenter Clinical Trial of the Effects of Topical Application of Cerium Nitrate/Silver Sulfadiazine Cream Versus Silver Sulfadiazine Cream Alone in the Treatment of Burn Patients, 9/26/00-present, \$31,500.00.

HGS KGF-2-WHO4-A Randomized, Double-blinded, Parallel-Group, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Repifermin (KGF-2) in Subjects with Venous Ulcers, 10/00-present, \$167,955.00. Co-investigator, Primary Investigator, Gloria Chin, MD.

Treatment of Diabetic Foot Ulcers With A Protease Inhibitor, Doxycycline, 11/15/00, \$150,000. VA Grant, Co-investigator, Primary Investigator, Gloria Chin, MD.

Protocol #AI 464-025: A Randomized, Double-blind, Multi-center, Comparative Phase III Study of Intravenous BMS-284756 with or without Oral BMS-284756 Follow-up vs Intravenous Piperacillin/Tazobactam with or without Oral Amoxicillin/Clavulanate Follow-up in the Treatment of Complicated Skin and Skin Structure Infections, 01/2001-complete, \$47,500.00.

A Multicenter, Retrospective Chart and Database Review of Patients Treated for Lightning Injury, 6/15/01-complete.

A Multicenter, Retrospective Chart and Database Review of Subjects with Purpura Fulminans, 6/16/01-4/23/02.

Microarray Analysis of Gene Expression in Pediatric and Adult Post-burn Hypertrophic Scars, International Association of Fire Fighters Burn Foundation, 2002-present, \$25,000.

A Dose Escalating Phase I Study of ADPDGF-BGAM in the Treatment of Diabetic Ulcers of the Lower Extremity, 8/2002-present, \$218,166.25.

Enzymatic Debridement in Burn Patients: A Comparison to Standard of Care, 12/06/02-present, \$ 34,440.00.

Evaluation of the Efficacy of the V.A.C. on Management of Acute Hand Burns, 1/6/03-present, \$37,563.00.

PUBLICATIONS

Publications

1. Schultz GS, Barillo DJ, Mozingo DW, Chin GA. Wound Bed Preparation and a Brief History of TIME. *International Wound Journal* 1(1)19-32, 2004.
2. Still J, Glat P, Silverstein P, Griswold J, Mozingo D. The Use of a Collagen Sponge/Living Cell Composite Material to Treat Donor Sites in Burn Patients. *Burns* 29(8)837-841, 2003.
3. Paddock HN, Schultz GS, Baker HV, Varela JC, Beierle EA, Moldawer LL, Mozingo DW. Analysis of Gene Expression Patterns in Human Postburn

Hypertrophic Scars. *J Burn Care & Rehab.* November/December 24(6)371-377, 2003.

4. Warner PM, Kagan RJ, Yakuboff KP, Kemalyan N, Palmieri TL, Greenhalgh DG, Sheridan RL, Mozingo DW, Heimback DM, Gibran NS, Engrav L, Saffle JR, Edelman LS, Warden DG. Current Management of Purpura Fulminans: A Multicenter Study. *J Burn Care & Rehab.* May/June 24(3)119-126, 2003.
5. Tasaki O, Mozingo DW, Dubick MA, Goodwin CW, Yantis LD, Pruitt BA Jr. Effects of Heparin and Lisofylline on Pulmonary Function After Smoke Inhalation Injury in an Ovine Model. *Crit Care Med.* 30(3) 637-643, 2002.
6. Dubick MA, Carden SC, Jordan BS, Langlinais PC, Mozingo DW. Indices of antioxidant status in rats subjected to wood smoke inhalation and/or thermal injury. *Toxicology.* 176 (2002) 145-157.
7. Palmiere, TL, Greenhalgh DG, Saffle JR, Spence RJ, Peck MD, Jeng JC, Mozingo DW, Yowler CJ, Sheridan RL, Ahrenholz DH, Caruso DM, Foster KN, Kagan RJ, Voight DW, Purdue GF, Hunt JL, Wolf S, Molitor F, *J Burn Care & Rehab* March/April 23(2) 87-96, 2002.
8. Harrington DT, Mozingo DW, Cancio L, Bird P, Jordan B, Goodwin CW. Thermally injured patients are at significant risk for thromboembolic complications. *J Trauma.* March 50(3) 495-499, 2001.
9. Fukuzuka K, Edwards CK III, Clare-Salzler M, Copeland EM III, Moldawer LL, Mozingo DW: Glucocorticoid and fas ligand induced mucosal lymphocyte apoptosis after burn injury, *J Trauma.* October 49 (4) 710-71, 2000.
10. Fukuzuka K, Edwards CK III, Clare-Salzler M, Copeland EM III, Moldawer LL, Mozingo DW: Glucocorticoid-induced, caspase-dependent organ apoptosis early after burn injury, *Am J Physiol Regulatory Integrative Comp Physio.* 278: R1005-R1018, 2000.
11. Tasaki O, Goodwin C, Mozingo DW, Cioffi WG Jr, Ishihara S, Brinkley WW, Dublick MA, Smith RH, Srivastava O, Pruitt BA Jr: Selectin blockage worsened lipopolysaccharide-induced lung injury in a swine model, *J Trauma.* June, 46(6): 1089-1095, 1999.
12. Ishihara S, Ward JA, Tasaki O, Brinkley WW, Seraile LG, Pruitt BA Jr, Mozingo DW: Effects of long-term hemofiltration on circulating mediators and superoxide production during continuous endotoxin administration, *J Trauma.* May, 46(5): 894-89, 1999.
13. Ishihara S, Ward JA, Tasaki O, Pruitt BA Jr, Javors MA, Cassidy RA, Mozingo DW: Biphasic changes in left ventricular function during hyperdynamic endotoxemia, *Am J Physiol.* May, 276(5 Pt2):R1516-R1524, 1999.
14. Fukuzuka K, Rosenberg JJ, Gaines GC, Edwards CK III, Clare-Salzler M, McKay LD, Moldawer LL, Copeland EM III, Mozingo DW: Caspase-3-dependent organ apoptosis early after burn injury, *Ann Surg.* 229(6), 1999.

15. Mozingo DW: Treatment of Burns, *Current Surgery*, Vol 55(6), July/August 1998.
16. Fukuzuka K, Moldawer LL, Mozingo DW: Increased organ apoptosis early after burn is limited to lymphoid tissues and is TNF α independent. American College of Surgeons, *Surgical Forum*, Vol XLIX: 102-104, 1998.
17. Ishihara S, Ward JA, Tasaki O, Pruitt BA Jr, Goodwin CW Jr, Mozingo DW, Cioffi WG Jr: Inhaled nitric oxide prevents left ventricular impairment during endotoxemia, *J Appl Physiol*. 85(6): 2018-24, 1998.
18. Tasaki O, Mozingo DW, Ishihara S, Brinkley WW, Johnson AA, Smith RH, Srivastava O, Mason AD, Pruitt BA Jr., Cioffi WG Jr: Effect of sulfo lewis C on smoke inhalation injury in an ovine model, *Crit Care Med*. 26(7): 1238-1243, 1998.
19. Yowler CW, Mozingo DW, Ryan JC, Pruitt BA Jr: Factors contributing to delayed extremity amputation in burn patients. *J Trauma*. 45(3): 522-526, 1998.
20. Tasaki O, Goodwin CW, Saitoh D, Mozingo DW, Ishihara S, Brinkley WW, Cioffi WG Jr, Pruitt BA Jr, Effects of burns on inhalation injury. *J Trauma* 43(4): 603-607, 1997.
21. Barillo DJ, Harvey KD, Hobbs CL, Mozingo DW, Cioffi WG, Pruitt BA Jr: Prospective outcome analysis of a protocol for the surgical and rehabilitative management of burns to the hands. *Plast. Reconstr. Surg.* 100: 1442, 1997.
22. Cancio LC, Mozingo DW, Pruitt BA Jr: Administering affective emergency care for severe thermal injuries. *J Crit Illness*. 12(2): 85-95, 1997.
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71. Mozingo DW, Cioffi WG, McManus WF, Pruitt BA Jr: Peritoneal lavage in the diagnosis of acute surgical abdomen following thermal injury. Proceedings of the 24th Annual Meeting of the American Burn Association, Salt Lake City, Utah, April 1992, page 146.
72. Mozingo DW, Becker WK, Lamiell JM, Cioffi WG, Pruitt BA Jr: Pulmonary amino acid flux in critically ill surgical patients. Proceedings of the International Surgical Week, Stockholm, Sweden, August 1991, abstract 859, page 433.
73. Mozingo DW, Becker WK, Mason AD, Pruitt BA Jr: The significance of jaundice in burn patients. Proceedings of the International Surgical Week, Stockholm, Sweden, August 1991, abstract 539, page 355.
74. Mozingo DW, Ducey JP, Lamielli JM, Gueller GE: The effect of 6% saline on cerebral hemodynamics following hemorrhage. Society of Critical Care Medicine, June 1990.
75. Mozingo DW, Alvarez JD: Spontaneous thoracobiliary fistula – a rare complication of an “asymptomatic” gallstone. The 42nd Annual Meeting of the Southwest Surgical Congress, April 1990.
76. Mozingo DW, Ducey JP, Lamielli JM, Gueller GE: The effect of 6% saline on cerebral hemodynamics following hemorrhage. Proceedings of the Society of Critical Care Medicine, New Orleans, Louisiana, 5-9 June 1989, 17(4) S147.
77. Mozingo DW, Missavage AE, McManus WF, Pruitt BA Jr: Acalculous cholecystitis diagnosed by Indium-III labeled leukocytic scanning in a severely burned patient. The 39th Annual Meeting of the Southwest Surgical Congress, April 1987.

Miscellaneous Publications

1. Mozingo DW: Quality improvement guidelines for burn center verification, <http://ameriburn.org/pub/verification.htm>, American Burn Association Web Page

EXHIBITS

1. McKinnon C, Dubose MA, Groher ME, Mann G, Mozingo, DW: Pattern of Dysphagia Recovery Following Thermal Burn Injury. Proceedings of the 12th Annual Dysphagia Research Society Meeting, San Francisco, CA 2-4 October, 2003.
2. Perrin KJ, Meyer CL, Manion KL, Roque DR, Langer KA, Wingard JR, Mozingo DW: Management of the cutaneous manifestations of graft vs. host disease using burn wound treatment protocols. Proceedings of the American Burn Association 33rd Annual Meeting, Boston, Massachusetts, 18-21 April 2001.
3. Ishihara S, Ward JA, Pruitt BA Jr, Mozingo DW: Comparison of two different parameters for elimination TNF_α from circulating blood by continuous hemofiltration during endotoxemia. Proceedings of the 29th Educational & Scientific Symposium Critical Care Medicine, Orlando, Florida, 11-15 February 2000.
4. Fukuzuka K, Moldawer LL, Mozingo DW: Increased organ apoptosis following burn injury. Proceedings of the 21st Annual Conference on Shock, San Antonio, TX, June 1998.
5. Ishihara S, Ward JA, Tasaki O, Brinkley WW, Seraile LG, Pruitt BA Jr, Mozingo DW: Effects of long term hemofiltration of endotoxin, cytokine, eicosanoid and superoxide production during sepsis. Proceedings of the AAST/JAAM Joint Meeting, Kamuela, Hawaii, September 24-27 1997.
6. Tasaki O, Goodwin CW, Mozingo DW, Brinkley WW, Dubick MA, Pruitt BA Jr: Effects of heparin and lisofylline on pulmonary function following severe smoke inhalation injury in an ovine model. Proceedings of the AAST/JAAM Joint Meeting, Kamuela, Hawaii, September 24-27 1997.
7. Ishihara S, Tasaki O, Pruitt B Jr, Cioffi W Jr, Ward J, Goodwin C, Mozingo D: Nitric oxide inhalation prevented left ventricular impairment in an awake porcine model simulating human septic shock. 17th Annual Meeting of the Surgical Infection Society. Pittsburgh, PA, 1-3 May 1997.
8. Allies WE, Mozingo DW, Pruitt BA Jr: Application of intrapulmonary percussive ventilation (IPV) therapy in patients with smoke inhalation. 28th Annual Meeting of the American Burn Association, 14-17 March 1996.
9. Cancio LC, Yowler CJ, Mozingo DW, Mason AD Jr, Pruitt BA Jr: Gastrointestinal surgery following thermal injury. 28th Annual Meeting of the American Burn Association, 14-17 March 1996.

10. Sirak RM, Hobbs CL, Mozingo DW, Yowler CJ, Pruitt BA Jr: The pediatric travois net bed: a cost effective alternative to specialty high air-flow beds. 28th Annual Meeting of the American Burn Association, 4-17 March 1996.
11. Barillo DJ, Stetz CK, Mozingo DW, Yowler CJ, Pruitt BA Jr: Preventable burns associated with the misuse of gasoline. 28th Annual Meeting of the American Burn Association, 14-17 March 1996.
12. Hobbs CL, Barillo DJ, Jarvey DW, Mozingo DW, Cioffi WG, McManus WF, Pruitt BA Jr: Physical and occupational therapy support of a burn mass casualty incident: planning implications for future incidents. 8th Annual Trauma Anesthesia and critical Care Symposium, Baltimore, Maryland, 11-13 May 1995.
13. Barillo DJ, Hidenrite D, Stetz CK, Greenfield E, Mozingo DW, McManus WF, Pruitt BA Jr: Occupational exposure to bloodborne pathogens in the burn center – a serologic study of burn patients. 8th Annual Trauma Anesthesia and Critical Care Symposium, Baltimore, Maryland, 11-13 May 1995.
14. Harvey KD, Barillo DJ, Hobbs CL, Mozingo DW, Cioffi WG, McManus WF, Pruitt BA Jr: Computer assisted evaluation of hand function following thermal injury. 27th Annual Meeting of the American Burn Association, Albuquerque, New Mexico, 19-22 April 1995.
15. Dubick MA, Janssen CM, Mozingo DW, Mason AD Jr, Pruitt BA Jr: Combined smoke inhalation and thermal injury augments changes in extrapulmonary antioxidant status in rats, 27th Annual Meeting of the American Burn Association, Albuquerque, New Mexico, 19-22 April 1995.
16. Allies WE, Mozingo DW, Fitzpatrick JC, Cioffi WG, McManus WF, Pruitt BA Jr: Increased humidification requirements of VDR ventilation. 27th Annual Meeting of the American Burn Association, Albuquerque New Mexico, 19-22 April 1995.
17. Mozingo DW, Rochon RB, Lamiell JM: The effect of dobutamine infusion on fluid volume requirements following hemorrhage. Annual Meeting of the Shock Society, Santa Fe, New Mexico, June 1993.
18. Mozingo DW, Becker WK, Cioffi WG Jr, McManus WF, Pruitt BA Jr: Pulmonary amino acid flux in critically ill surgical patients. International Surgical Week, Stockholm, Sweden, 25-31 August 1991.
19. Mozingo DW, Missavage AE, McManus WF, Pruitt BA Jr: Acalculous cholecystitis diagnosed by Indium -III labeled leukocyte scanning in a severely burned patient. 39th Annual Meeting of the Southwest Surgical Congress, Coronado, California, 16-29 April 1987.

INVITED PRESENTATIONS

1. New Technologies and Burns. Florida Surgical Society 2004 Annual Meeting, Key West, Florida, 25-27 June 2004.

2. Initial Burn Care. Holmes Regional Medical Center, 4 June 2004.
3. Funding for Burn Disaster Preparedness. 36th Annual Meeting of the American Burn Association, Vancouver, British Columbia, 25 March 2004.
4. Advances in Burn Care. Alachua County Medical Society, Gainesville, FL, 9 March 2004.
5. Burn Injury. Anatomy Grand Rounds Fall 03 for 1st year medical students, University of Florida, Gainesville, FL, 29 August 2003.
6. Regulating Healing: From Burns to Chronic Wounds. Wound Healing Symposium, University of Florida, Gainesville, Florida, 23 July 2003.
7. Burn Care for the Unburned. Grand Rounds, Temple University, Department of Surgery, Philadelphia, Pennsylvania, 14 May 2003.
8. The Resident Shortage: Latest Strategies. Sunrise Symposium at the 35th Annual Meeting of the American Burn Association, Miami Beach, Fl, 3 April 2003.
9. Molecular Approaches for Regulating Wound Healing. University of Florida Genetics Institute Seminar, Gainesville, Fl, 04 March 2003.
10. Adrenal Insufficiency in the SICU Setting. University of Florida Continuing Medical Education, Department of Surgery, Gainesville, Fl, January 23, 2003.
11. Updates on Burn Care. Proceedings of the 48th Clinical Meeting of the Frederick A. Coller Surgical Society, Sea Island, Ga, 19 October 2002.
12. Comparison of the Biomechanical Properties of Burns Grafted with Conventional Split Thickness Skin vs. Integra™ Artificial Skin. Proceedings of the 11th Quadrennial Congress of the International Society for Burn Injuries, Seattle, Washington, 11-16 August 2002.
13. The Effect of Silver-Coated Antimicrobial Dressings on Matrix Metalloprotease (MMP) Levels in Lower Extremity Venous Stasis Ulcers, Smith & Nephew Advanced Wound Care Exhibit Symposium, Chicago, Illinois, American Burn Association Annual Meeting, 26 April 2002.
14. Comparison of the Biomedical Properties of Burns Grafted with Conventional Split-thickness Graft vs. Integra®, American Burn Association Satellite Symposium, Chicago, Illinois, 25 April 2002.
15. Burn Center Verification, Sunrise Symposia. Proceedings of the American Burn Association 34th Annual Meeting, Chicago, Illinois, 25 April 2002.
16. Burns in the Very Obese, Educational Symposium, American Burn Association 34th Annual Meeting, Chicago, Illinois, 24 April 2002.

17. Improved Functional Outcome of Skin Grafting for Major Burns Using Dermal Regeneration Technology, Edward M. Copeland III, MD Scientific Symposium, 1 March 2002.
18. Initial Management of Burns, University of Florida Trauma Lecture Series, Gainesville, Florida, 17 January 2002.
19. Burn Resuscitation, Critical Care & Emergency Medicine 2001, Lake Buena Vista, Florida, 21 November, 2001.
20. Wound Bed Preparation, Smith & Nephew Conference, Atlanta, Georgia, 8 November, 2001.
21. Quemaduras Eléctricas (Electrical Injury), 9 Congreso Argentino de Quemaduras 2001, Buenos Aires, Argentina, 14 June 2001.
22. Nutrición del Paciente Quemado (Nutrition in Burn Patients), 9 Congreso Argentino de Quemaduras 2001, Buenos Aires, Argentina, 13 June 2001.
23. Tecnología de Reemplazo Dérmico (Dermal Regeneration Technology), 9 Congreso Argentino de Quemaduras 2001, Buenos Aires, Argentina, 12 June 2001.
24. Lesión inhalatoria (Inhalation Injury), 9 Congreso Argentino de Quemaduras 2001, Buenos Aires, Argentina, 12 June 2001.
25. Síndrome de necrosis epidermica toxica (Toxic Epidermal Necrolysis Syndrome), 9 Congreso Argentino de Quemaduras 2001, Buenos Aires, Argentina, 11 June 2001.
26. Caring for Burns in the Outpatient Setting, The 14th Annual Symposium on Advanced Wound Care & Medical Research Forum on Wound Repair, Las Vegas, Nevada, 1 May 2001.
27. Wound Bed Preparation, Smith & Nephew Conference, Jacksonville, FL 22 May 2001.
28. Burn Care for the UnBurned, Surgical Grand Round, Cook County Hospital, Chicago, IL, 17 May 2001.
29. Wound Bed Preparation, Smith & Nephew Conference, Chicago, IL, 17 May 2001.
30. Treating Inhalation Injuries, Sunrise Symposium breakfast session, 2001 American Burn Association Meeting, Boston, MA, 19 April 2001.
31. Burn Rehabilitation, Rehab 2001: From Discovery to Recovery, Gainesville, Florida, 11 April 2001.
32. Wound Bed Preparation, Smith & Nephew Wound Conference, Atlanta, GA, 14 December 2000.

33. What's New In Burn Management, Trauma Multidisciplinary Conference, Holmes Regional Medical Center, 7 September 2000.
34. What's New In Burn Management, General Staff CME Conference, Holmes Regional Medical Center, 8 September 2000.
35. Burns, Surgical Basic Science Conference, University of Florida College of Medicine, Gainesville, FL, 6 July 2000.
36. What's New In Burn Management, 2000 Joint Annual Meeting Florida Chapter and South Florida Chapter American College of Surgeons, Palm Beach, FL, 24 June 2000.
37. Thermal Injury, Union County EMS, Lake Butler, FL, 21 June 2000.
38. ATLS Provider Course, University of Florida, Jacksonville, FL, 14 April 2000.
39. Chemical Burns, 32nd Annual Meeting American Burn Association, Las Vegas, NV, 14 March 2000. Thermal Injury, University of Florida Tissue Bank, Gainesville, FL, 29 March 2000.
40. Electric Injury, Putnam Power Plant, Palatka, Florida, 23 March 2000.
41. Electric Injury, Florida Power and Light Seminar, Lake City, Florida, 9 February 2000.
42. Electric Injury, Florida Power and Light Seminar, Palatka, Florida, 16 February 2000.
43. Electric Injury, Florida Power and Light Seminar, St. Augustine, Florida, 23 February 2000.
44. Electric Injury, Florida Power and Light Seminar, St. Johns Service Center, Palatka, Florida, 23 February 2000.
45. Severe Soft Tissue Infection Requiring ICU Care, Critical Care and Emergency Medicine 1999, Lake Buena Vista, FL, 24 November 1999.
46. Diagnostico y tratamiento de la lesion inhalatoria (Diagnosis and Treatment of Inhalation Injury), III Congreso Latinoamericano de Quemaduras, VII Congreso Venezolano de Quemaduras, Puerto La Cruz, Venezuela, 19-23 October 1999.
47. Quemaduras (Burns), VII Congreso Venezolano de Quemaduras, Puerto La Cruz – Venezuela, 19-23 October 1999.
48. ATLS Provider Course. University of Florida, Gainesville, FL, 9 September 1999.
49. New Treatments for Burn Wounds. 2nd Annual Wound Care Symposium. Gainesville, FL, 19 April 1999.

50. Innovations in Wound Care. 31st Annual Meeting American Burn Association, Orlando, FL, 25 March 1999.
51. Faculty, ABLS Instructor Course. 31st Annual Meeting American Burn Association, Orlando, FL, 24 March 1999.
52. Initial Assessment of Burn Injured Patients. ABLS Provider Course, Gainesville, FL, 3 December 1998.
53. Nutritional Support for Severely Burned Patients: XI Congreso Panamericano del Trauma, III Congreso Argentino de Trauma, Buenos Aires, Argentina, 12 November 1998.
54. Geriatric Patients with Deep and Extensive Burns: Early Escharectomy? XI Congreso Panamericano de Trauma, III Congreso Argentino de Trauma, Buenos Aires, Argentina, 12 November 1998. Burns.
55. Fluid Resuscitation of Burn Injury. ABLS provider course. Richmond, VA, 10 October 1998. Initial Burn Management. Doctors' Memorial Hospital. Perry, FL, 1 October 1998.
56. Biomedical Applications in Burn Therapy. University of Florida Biomedical Engineering Course, Gainesville, FL, 6 October 1998.
57. Advanced Trauma Life Support Course. Jacksonville, FL, 16-17 July 1998.
58. Treatment After Inhalation of Toxic Substances, Critical Care & Emergency Medicine 1998, Lake Buena Vista, FL, 21-15 November 1998.
59. Current Burn Care. Grand Rounds, University of Florida Rehabilitation Services, Gainesville, FL, 10 March 1998.
60. Burn Wounds in the Community. First Annual Wound Care Symposium, Gainesville, FL, 2 February 1998.
61. Burn Center Care and Organization. The Rotary Club of Gainesville, Sunrise. Gainesville, FL, 19 February 1998.
62. Burn Care Strategies. Critical Care Update Seminar, Orlando, FL, 25 November 1997.
63. Post-op Trauma Problems. Critical Care Update Seminar, Orlando, FL, 25 November 1997.
64. Perioperative antibiotics in burn surgery. U.S. Army Institute of Surgical Research, 50th Anniversary Symposium, San Antonio, TX, 30 October-2 November 1997.

65. Management of Penetrating Trauma. Burn and Critical Care Symposium, Managua, Nicaragua, 13-15 October 1997.
66. Initial Management of Blunt Trauma. Burn and Critical Care Symposium, Managua, Nicaragua, 13-15 October 1997.
67. Electric Injury. Burn and Critical Care Symposium, Managua, Nicaragua, 13-15 October 1997.
68. Thermal Injury. Burn and Critical Care Symposium, Managua, Nicaragua, 13-15 October 1997.
69. Injuries Due to Burns and Cold. Advanced Trauma Life Support Course. Jacksonville, FL, September 12 1997.
70. Determinants of the Hypermetabolic Response. 37th World Congress of Surgery, International Surgical Week 97, Acapulco, Mexico, 24-20 August 1997.
71. Manejo del Dolor en el Paciente Quemado (Pain Management in Burned Patients). VI Congreso Venezolano de Quemaduras, Ciudad Bolivar, Venezuela, 24-26 July 1997.
72. Manejo Quirúrgico del Quemado (Surgical Management of Burns). VI Congreso Venezolano de Quemaduras. Ciudad Bolivar, Venezuela, 24-26 July 1997.
73. Papel de la Excisión Temprana del Tejido Quemado Efecto en la Sobrevida (Early Excision of Burns and Effect on Survival), VI Congreso Venezolano de Quemaduras. Ciudad Bolivar, Venezuela, 24-26 July 1997.
74. Manejo de la Fase Aguda del Quemado (Fluid Resuscitation in Burn Patients. VI Congreso Venezolano de Quemaduras, Ciudad Bolivar, Venezuela, 24-26 July 1997.
75. Antimicrobianos de uso Tópico, Futuro y Resistencia Bacteriana (The Use of Topical Antimicrobial Agents and Development of Resistant Bacteria). VI Congreso Venezolano de Quemaduras, Ciudad Bolivar, Venezuela, 24-26 July 1997.
76. Lesión Inhalatoria y Manejo Crítico (Inhalation Injury and Critical Care Management). VI Congreso Venezolano de Quemaduras, Ciudad Bolivar, Venezuela, 24-26 July 1997.
77. Manejo de la Fase Aguda de las Quemaduras in Ninos (Fluid Resuscitation in Pediatric Burn Patients). VI Congreso Venezolano de Quemaduras, Ciudad Bolivar, Venezuela, 24-26 July 1997.
78. Smoke Inhalation Injury: Diagnosis and Treatment. Surgical Grand Rounds, University of Florida, Department of Surgery, Gainesville, FL, 9 April 1997.
79. New Techniques of Mechanical Ventilation. Sunrise Symposium at the 29th Annual Meeting of the American Burn Association, New York, NY, 22 March

1997.

80. Thrombosis Prophylaxis: Should we be filtering or anticoagulating our patients? The 29th Annual Meeting of the American Burn Association, New York, NY, 21 March 1997.
81. Practical Pulmonary Physiology. University of North Dakota, Surgical Residents Seminar, Grand Forks, ND, 29 January 1997.
82. Burn Wound Closure: A Search for the Holy Grail. Medical Staff Grand Rounds, University of North Dakota, Grand Forks, ND, 29 January 1997.
83. Burn Center Verification 9th Annual Regional Burn Seminar, Charleston, SC, 6-8 December 1996.
84. Toxic Epidermal Necrolysis Syndrome, University of Florida Department of Surgery Grand Rounds, Gainesville, FL, 4 December 1996.
85. Difficult Surgical Problems. Critical Care Update Seminar, Orlando, FL, 25-26 November 1996.
86. Initial Trauma Care. Critical Care Update Seminar, Orlando, FL 25-26 November 1996.
87. Resuscitation of the Burn Patient, University of Florida, Critical Care Update Seminar, Orlando, FL, 25-26 November 1996.
88. Ethical Decision Making in Burn Care. First Annual San Antonio Trauma Symposium, San Antonio, TX, 16-17 September 1996.
89. Progress in Burn Care, University of Florida, Department of Surgery Grand Rounds, Gainesville, FL, 25 September 1996.
90. Cost Effectiveness of Cultured Epidermal Autografts in Burn Patients. Annual Meeting of the Wound Healing Society, Boston, MA, 16-19 May 1996.
91. Pulmonary Assessment of the Burned Patient. 28th Annual Meeting of the American Burn Association, Nashville, TN, 7-10 March 1996.
92. The Burn Patient with Co-morbid Factors. 28th Annual Meeting of the American Burn Association, Nashville, TN, 7-10 March 1996.
93. Mission of the U.S. Army Institute of Surgical Research, Alamo Federal Executive Board Leadership Course, Fort Sam Houston, TX, 10 January 1996.



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ISBN: 1-56363-330-2

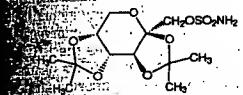
INFORMATION

McNEIL LABORATORIES, Inc.
PA 19477

643-10-089-2

Product Identification Guide, page 329

INDICATIONS
 Topiramate is a sulfamate-substituted monosaccharide that is used as an antiepileptic drug. TOPAMAX® (topiramate capsules) Sprinkle Capsules are available as 15 mg sprinkle capsules for oral administration as capsules or for opening and sprinkling onto soft food. It is a white crystalline powder with a bitter taste. It is soluble in alkaline solutions containing bicarbonate or sodium phosphate and having a pH of 6.5. It is only soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/g saturated solution has a pH of 6.3. Topiramate has the formula $C_{12}H_{21}NO_3S$ and a molecular weight of 234.5. Topiramate is designated chemically as: 2,3,4,5-tetrahydro-2-methyl-2H,4H-pyran-2,3-dione, 4-(methylsulfonyl)amino-4H-1,2-dihydro-3H-pyran-3-carboxylic acid.



(topiramate capsules) Sprinkle Capsules contain coated beads in a hard gelatin capsule. The capsules are sugar spheres (sucrose and starch), calcium acetate, gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical grade.

PHARMACOLOGY

Action: The mechanism by which topiramate exerts its anticonvulsant effect is unknown; however, electrophysiological studies of the effects of topiramate on cultured hippocampal slices have revealed three properties that may contribute to topiramate's antiepileptic efficacy. First, action potentials repetitively by a sustained depolarization that are blocked by topiramate in a time-dependent manner, suggestive of a voltage-dependent sodium channel blocker. Second, topiramate increases the frequency of GABA_A activation (GABA_A receptor). It enhances the ability of GABA to induce a flux of ions into neurons, suggesting that topiramate increases the activity of this inhibitory neurotransmitter. It is not blocked by flumazenil, a benzodiazepine antagonist. Third, topiramate increases the duration of the GABA_A receptor-mediated differentiation of topiramate from barbiturates at the GABA_A receptor. Third, topiramate increases the ability of kainate to activate the kainate/5-hydroxy-5-methylisoxazole-4-propionic acid (HIMBA) subtype of excitatory amino acid (glutamate) receptors (NMDA) at the NMDA receptor subunits. The effects of topiramate are concentration-dependent, in the range of 1 μ M to 200 μ M. This pharmacologic effect is generally similar to that of acetazolamide, a known carbonic anhydrase inhibitor, and is not thought to be a major contribution to topiramate's antiepileptic activity.

Anticonvulsant activity in rodent models: Topiramate is effective in blocking clonic seizures induced by pentylenetetrazole. It is also effective in rodent models of epilepsy, including tonic and absence-like seizures in the spontaneous (SERT) and tonic and clonic seizures induced by kindling of the amygdala or by global ischaemia.

bioequivalence: Topiramate is bioequivalent to the immediate release formulation and, therefore, may be substituted for it.

kinetics: The bioavailability of topiramate from capsules is about 80% compared to a solution. The bioavailability of topiramate is not affected by food.

absorption: The absorption of topiramate is linear with dose and is complete in the gut. The mean plasma half-life is 21 hours after single or multiple doses. It is thus reached in about 4 days in patients with normal renal function. Topiramate is 13-17% bound to plasma proteins over the concentration range of 0.1 to 200 mg/L.

metabolism: The metabolism of topiramate is not affected by food.

excretion: The excretion of topiramate is linear with dose and is complete in the gut. The mean plasma half-life is 21 hours after single or multiple doses. It is thus reached in about 4 days in patients with normal renal function. Topiramate is 13-17% bound to plasma proteins over the concentration range of 0.1 to 200 mg/L.

hemodialysis: Topiramate is cleared by hemodialysis. Using a high efficiency, counterflow, single pass-dialysis hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20-30 mL/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialysis period.

Table 1: Topiramate Dose Summary During the Stabilization Periods of Each of Five Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Dose Stabilization	Placebo*	Target Topiramate Dosage (mg/day)				
			200	400	600	800	1,000
YD	N	42	42	40	41	—	—
	Mean Dose	5.9	200	390	556	—	—
	Median Dose	6.0	200	400	600	—	—
YE	N	44	—	—	40	45	40
	Mean Dose	9.7	—	—	544	739	796
	Median Dose	10.0	—	—	600	800	1,000
Y1	N	23	—	19	—	—	—
	Mean Dose	3.8	—	395	—	—	—
	Median Dose	4.0	—	400	—	—	—
Y2	N	30	—	—	28	—	—
	Mean Dose	5.7	—	—	522	—	—
	Median Dose	6.0	—	—	600	—	—
Y3	N	28	—	—	—	25	—
	Mean Dose	7.9	—	—	—	568	—
	Median Dose	8.0	—	—	—	600	—

*Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol Y1, 4 tablets/day; Protocol YD and Y2, 6 tablets/day; Protocol Y3, 8 tablets/day; YE, 10 tablets/day.

Table 2: Median Percent Seizure Rate Reduction and Percent Responders in Five Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Efficacy results	Placebo	Target Topiramate Dosage (mg/day)				
			200	400	600	800	1,000
YD	N	45	45	45	46	—	—
	Mean % Reduction	11.6	27.2 ^a	47.5 ^b	44.7 ^c	—	—
	% Responders	18	24	44 ^d	46 ^d	—	—
YE	N	47	—	—	48	48	47
	Median % Reduction	1.7	—	—	40.8 ^e	41.0 ^e	36.0 ^e
	% Responders	9	—	—	40 ^f	41 ^f	38 ^f
Y1	N	24	—	23	—	—	—
	Median % Reduction	1.1	—	40.7 ^g	—	—	—
	% Responders	8	—	35 ^g	—	—	—
Y2	N	30	—	—	30	—	—
	Median % Reduction	12.2	—	—	46.4 ^h	—	—
	% Responders	10	—	—	47 ^h	—	—
Y3	N	28	—	—	—	28	—
	Median % Reduction	20.6	—	—	—	24.3 ⁱ	—
	% Responders	0	—	—	—	43 ⁱ	—

Comparisons with placebo: ^ap = 0.080; ^bp = 0.010; ^cp = 0.001; ^dp = 0.050; ^ep = 0.065; ^fp = 0.005.

lution, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in humans following oral administration.

Pharmacokinetic Interaction (see also Drug Interactions): Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized under PRECAUTIONS (Table 3).

Special Populations:

Renal Impairment:

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30-69 mL/min/1.73m²) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m²) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m²). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramates not predicted by creatinine clearance. In general, however, use of one-half the usual dose is recommended in patients with moderate or severe renal impairment.

Hamodialysis:

Topiramate is cleared by hemodialysis. Using a high efficiency, counterflow, single pass-dialysis hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20-30 mL/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialysis period.

Age, Gender, and Race:

Clearance of topiramate was not affected by age (18-67 years), gender, or race.

Pediatric Pharmacokinetics:

Pharmacokinetics of topiramate were evaluated in patients ages 4 to 17 years receiving one or two other antiepileptic drugs. Pharmacokinetic profiles were obtained after one week at doses of 1, 3, and 9 mg/kg/day. Clearance was independent of dose. Although the relationship between age and clearance among patients of pediatric age has not been systematically evaluated, it appears that the weight-adjusted clearance of topiramate is 50% higher in pediatric patients than in adults.

CLINICAL STUDIES

The studies described in the following section were conducted using TOPAMAX® (topiramate) Tablets. The effectiveness of topiramate as an adjunctive treatment for partial onset seizures was established in five multicenter, randomized, double-blind, placebo-controlled trials, two comparing several dosages of topiramate and placebo and three comparing a single dosage with placebo, in patients with a history of partial onset seizures, with or without secondarily generalization.

Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® Tablets or placebo. In each study, patients were stabilized on optimum dosages of their concomitant AEDs during an 8-12 week baseline phase. Patients who experienced at least 12 (or 8 for 8-week baseline studies) partial onset seizures, with or without secondarily generalization, during the baseline phase were randomly assigned to placebo or a specified dose of TOPAMAX® Tablets in addition to their other AEDs. Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. After titration, patients entered an 8 or

Topamax—Cont.

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. Responder rate (fraction of patients with at least a 50% reduction) was also measured. The median percent reductions in seizure rates and the responder rates by treatment group for each study are shown in Table 2. [See table 2 on previous page]

Subset analyses of the antiepileptic efficacy of TOPAMAX® Tablets in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

INDICATIONS AND USAGE

TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for the treatment of adults with partial onset seizures.

CONTRAINDICATIONS

TOPAMAX® (topiramate capsules) Sprinkle Capsules are contraindicated in patients with a history of hypersensitivity to any component of this product.

WARNINGS**Withdrawal of AEDs**

Antiepileptic drugs, including TOPAMAX®, should be withdrawn gradually to minimize the potential of increased seizure frequency.

Cognitive/Neuropsychiatric Adverse Events

Adverse events most often associated with the use of TOPAMAX® were central nervous system-related. The most significant of these can be classified into two general categories: 1) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties and 2) somnolence or fatigue. Additional non-specific CNS effects occasionally observed with topiramate as add-on therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances (e.g., irritability and depression). Reports of psychomotor slowing, speech and language problems, and difficulty with concentration and attention were common. Although in some cases these events were mild to moderate, they at times led to withdrawal from treatment. The incidence of psychomotor slowing is only marginally dose-related, but both language problems and difficulty with concentration or attention clearly increased in frequency with increasing dosage in the five double-blind trials (see ADVERSE REACTIONS, Table 5).

Somnolence and fatigue were the most frequently reported adverse events during clinical trials with TOPAMAX®. These events were generally mild to moderate and occurred early in therapy. While the incidence of somnolence does not appear to be dose-related, that of fatigue increases at doses above 400 mg/day.

Sudden Unexplained Death in Epilepsy (SUDEP)

During the course of premarketing development of TOPAMAX® (topiramate) Tablets, 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2,796 subject years of exposure).

This represents an incidence of 0.0035 deaths per patient year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving TOPAMAX® (ranging from 0.0005 for the general population of patients with epilepsy, to 0.003 for a clinical trial population similar to that in the TOPAMAX® program, to 0.005 for patients with refractory epilepsy).

PRECAUTIONS**General:****Kidney Stones**

A total of 322,086 (1.5%) of patients exposed to topiramate during its development reported the occurrence of kidney stones, an incidence about 2-4 times that expected in a similar, untreated population. As in the general population, the incidence of stone formation among topiramate treated patients was higher in men.

An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a weak carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of TOPAMAX® with other carbonic anhydrase inhibitors may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

Paresthesia

Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®.

Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required (see DOSAGE AND ADMINISTRATION).

Information for Patients:

Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation (see PRECAUTIONS: General, for support regarding hydration as a preventative measure).

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

Please refer to the end of the product labeling for important information on how to take TOPAMAX® (topiramate capsules) Sprinkle Capsules.

Drug Interactions:**Antiepileptic Drugs**

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized in the following table:

In Table 3, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added.

The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX® was given alone.

Table 3: Summary of AED Interactions with TOPAMAX®

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase ^a	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide ^b	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE

^a = Plasma concentration increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin.

^b = Is not administered but is an active metabolite of carbamazepine.

NC = Less than 10% change in plasma concentration.

AED = Antiepileptic drug.

NE = Not Evaluated.

Other Drug Interactions

Digoxin: In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established.

CNS Depressants: Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In a pharmacokinetic interaction study with oral contraceptives using a combination product containing norethindrone and ethinyl estradiol, TOPAMAX® did not significantly affect the clearance of norethindrone. The mean oral clearance of ethinyl estradiol at 800 mg/day dose was increased by 47% (range: 13-107%). The mean total exposure to the estrogenic component decreased by 18%, 21%, and 30% at daily doses of 200, 400, and 800 mg/day, respectively. Therefore, efficacy of oral contraceptives may be compromised by topiramate. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns. The effect of oral contraceptives on the pharmacokinetics of topiramate is not known.

Others: Concomitant use of TOPAMAX®, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided.

Laboratory Tests: There are no known interactions of topiramate with commonly used laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 0.5 to 1 times steady state exposures measured in patients receiving topiramate monotherapy at the recommended human dose (RHD) of 400 mg, and 1.5 to 2 times steady state topiramate exposures in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 3 times the RHD on a

lymphoma assay; it did not increase unscheduled DNA synthesis in rat hepatocytes *in vitro*; and it did not cause chromosomal aberrations in human lymphocytes in rat bone marrow *in vivo*. No adverse effects on male or female fertility were seen in rats at doses up to 100 mg/kg (2.5 times the RHD on a mg/m² basis).

Pregnancy: Pregnancy Category C

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animals. When oral doses of 20, 100, or 500 mg/kg were administered to pregnant mice during the period of organ formation, the incidence of fetal malformations (primarily craniofacial) was increased at all doses. The low dose was approximately 0.2 times the recommended human dose (RHD) on a mg/m² basis. Fetal body weights and ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg, 2.5, 30 and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased in the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m² basis) or greater during the organ formation period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural anomalies) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m² basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater. In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 100 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m² basis) or greater, and teratogenic effects (primarily vertebral malformations) were observed at 120 mg/kg (3 times the RHD on a mg/m² basis). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and mortality) was seen at 35 mg/kg and above. When females were treated during the latter part of gestation throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 times the RHD on a mg/m² basis) and reductions in pre- and/or postnatal body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m² basis) and above.

Maternal toxicity (decreased body weight gain; clinical signs) was evident at 100 mg/kg or greater.

In a rat embryo/fetal development study with a positive component (0.2, 2.5, 30 or 400 mg/kg during organogenesis), noted above, pups exhibited delayed physical development at 400 mg/kg (10 times the RHD on a mg/m² basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m² basis) and higher.

There are no studies using TOPAMAX® in pregnant women. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risks to fetus.

In post-marketing experience, cases of hypospadias have been reported in male infants exposed *in utero* to topiramate, with or without other anticonvulsants; however, causal relationship with topiramate has not been established.

Labor and Delivery:

In studies of rats where dams were allowed to deliver *in utero*, no drug-related effects on gestation length or parturition were observed at dosage levels up to 200 mg/kg. The effect of TOPAMAX® on labor and delivery in humans is unknown.

Nursing Mothers:

Topiramate is excreted in the milk of lactating rats. It is not known if topiramate is excreted in human milk. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to TOPAMAX® is unknown, the potential benefit to the mother should be weighed against the potential risk to the infant when considering recommendations regarding nursing.

Pediatric Use:

Safety and effectiveness in children have not been established. The pharmacokinetic profile of TOPAMAX® was studied in patients between the ages of 4 and 17 years.

CLINICAL PHARMACOLOGY; Pediatric Pharmacokinetics:**Gastric Use:**

In clinical trials, 2% of patients were over 60. No age difference in effectiveness or adverse effects were seen. There were no pharmacokinetic differences related to age alone, although the possibility of age-associated renal functional abnormalities should be considered.

Race and Gender Effects:

Evaluation of efficacy and safety in clinical trials has shown no race or gender related effects.

ADVERSE REACTIONS

The data described in the following section were obtained using TOPAMAX® (topiramate) Tablets. The most commonly observed adverse events associated with the use of topiramate at dosages of 200 to 400 mg/day in controlled trials, that were seen at greater frequency in topiramate-treated patients and did not appear to be dose-related were: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor

Table 4: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials^{a,b}
(Events that occurred in at least 1% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients)

Body System/ Adverse Event ^c	TOPAMAX® Dosage (mg/day)		
	Placebo (N=174)	200–400 (N=113)	600–1,000 (N=247)
Body as a Whole – General Disorders			
Asthenia	1.1	8.0	4.5
Back Pain	4.0	6.2	2.0
Chest Pain	2.3	4.4	2.0
Influenza-Like Symptoms	2.9	3.5	3.2
Leg Pain	2.3	3.5	2.4
Hot Flushes	1.7	2.7	0.8
Body Odor	0.0	1.8	0.0
Edema	1.1	1.8	1.2
Rigors	0.0	1.8	0.4
Central & Peripheral Nervous System Disorders			
Dizziness	14.4	28.3	32.4
Ataxia	6.9	21.2	17.0
Speech Disorders/ Related Speech Problems	2.9	16.8	13.8
Nystagmus	11.5	15.0	15.0
Paresthesia	3.4	15.0	14.6
Tremor	6.3	10.6	13.8
Language Problems	0.6	6.2	11.7
Coordination Abnormal	1.7	5.3	3.6
Hypoesthesia	1.1	2.7	0.8
Gastrointestinal System Disorders			
Nausea	6.3	11.5	13.8
Dyspepsia	5.2	8.0	5.7
Abdominal Pain	2.9	5.3	7.3
Constipation	0.6	5.3	3.2
Dry Mouth	1.1	2.7	3.2
Gingivitis	0.0	1.8	0.4
Hearing and Vestibular Disorders			
Hearing Decreased	1.1	1.8	1.6
Metabolic and Nutritional Disorders			
Weight Decrease	2.3	7.1	12.6
Musculoskeletal System Disorders			
Myalgia	1.1	1.8	1.2
Platelet, Bleeding and Clotting Disorders			
Epistaxis	1.1	1.8	0.8
Psychiatric Disorders			
Somnolence	10.3	30.1	25.9
Psychomotor Slowing	2.3	16.8	25.1
Nervousness	7.5	15.9	20.6
Difficulty with Memory	2.9	12.4	12.6
Confusion	5.2	9.7	15.0
Depression	6.3	8.0	13.4
Difficulty with Concentration/Attention	1.1	8.0	15.4
Anorexia	4.0	5.3	11.3
Agitation	1.7	4.4	4.0
Mood Problems	1.7	3.5	10.1
Aggressive Reaction	0.6	2.7	4.0
Apathy	0.0	1.8	4.5
Depersonalization	0.6	1.8	1.6
Emotional Lability	1.1	1.8	2.4
Reproductive Disorders, Female			
Breast Pain, Female	0.0	8.3	0.0
Dysmenorrhea	2.6	8.3	0.0
Menstrual Disorder	0.0	4.2	0.0
Respiratory System Disorders			
Upper Respiratory Infection	11.5	12.4	12.1
Pharyngitis	2.9	7.1	2.8
Sinusitis	4.0	4.4	4.0
Dyspnea	1.1	1.8	3.2
Skin and Appendages Disorders			
Rash	4.0	4.4	3.2
Pruritus	1.1	1.8	3.2
Sweating Increased	0.0	1.8	0.4
Urinary System Disorders			
Hematuria	0.6	1.8	0.8
Vision Disorders			
Diplopia	6.3	14.2	14.6
Vision Abnormal	2.9	14.2	10.5
Eye Pain	1.1	1.8	2.0
White Cell and RBC Disorders			
Leukopenia	0.6	2.7	1.6

Topamax—Cont.

tase increased, dehydration, hypocalcemia, hyperlipemia, acidosis, hyperglycemia, creatinine increased, hyperchloremia, xerophthalmia. *Rare:* diabetes mellitus, hypernatremia, abnormal serum folate, hyponatremia, hypcholesterolemia, hypoglycemia, hypophosphatemia.

Musculoskeletal System Disorders: *Frequent:* orthralgia, muscle weakness. *Inrequent:* arthrosis, osteoporosis.

Myo-, Endo-, Pericardial & Verte Disorders: *Inrequent:* angina pectoris.

Neoplasms: *Inrequent:* basal cell carcinoma, thrombocythemia. *Rare:* polycythemia.

Platelet, Bleeding, and Clotting Disorders: *Inrequent:* gingival bleeding, purpura, thrombocytopenia, pulmonary embolism.

Psychiatric Disorders: *Frequent:* insomnia, personality disorder, impotence, hallucination, euphoria, psychosis, libido decreased, suicide attempt. *Inrequent:* paranoid reaction, appetite increased, delusion, paranoia, delirium, abnormal dreaming, neurosis. *Rare:* libido increased, manic reaction.

Red Blood Cell Disorders: *Frequent:* anemia. *Rare:* marrow depression, pancytopenia.

Reproductive Disorders, Female: *Frequent:* intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis, amenorrhea.

Reproductive Disorders, Male: *Inrequent:* ejaculation disorder, breast discharge.

Respiratory System Disorders: *Frequent:* coughing, bronchitis. *Inrequent:* asthma, bronchospasm. *Rare:* laryngitis.

Skin and Appendages Disorders: *Frequent:* acne, alopecia. *Inrequent:* dermatitis, nail disorder, folliculitis, dry skin, urticaria, skin discoloration, eczema, photosensitivity reaction, erythematous rash, seborrhea, sweating decreased, abnormal hair texture. *Rare:* chloasma.

Special Senses Other, Disorders: *Frequent:* taste perversion. *Inrequent:* taste loss, parosmia.

Urinary System Disorders: *Frequent:* urinary tract infection, micturition frequency, urinary incontinence, dysuria, renal calculus. *Inrequent:* urinary retention, face edema, renal pain, nocturia, albuminuria, polyuria, oliguria.

Vascular (Extracardiac) Disorders: *Inrequent:* flushing, deep vein thrombosis, phlebitis. *Rare:* vasospasm.

Vision Disorders: *Frequent:* conjunctivitis. *Inrequent:* abnormal accommodation, photophobia, abnormal lacrimation, strabismus, color blindness, myopia, mydriasis. *Rare:* cotsact, corneal opacity, iritis.

White Cell and Reticuloendothelial System Disorders: *Inrequent:* lymphadenopathy, eosinophilia, lymphopenia, granulocytopenia, lymphocytosis.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of TOPAMAX® has not been evaluated in human studies.

OVERDOSAGE

In acute TOPAMAX® overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has not been shown to adsorb topiramate *in vitro*. Therefore, its use in overdose is not recommended. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdosage reported, hemodialysis has not been necessary.

DOSAGE AND ADMINISTRATION

In the controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and clinical efficacy. No evidence of tolerance has been demonstrated in humans. Doses above 400 mg/day (600, 800, and 1000 mg/day) have not been shown to improve response.

The recommended total daily dose of TOPAMAX® (topiramate capsules) as adjunctive therapy is 400 mg/day in two divided doses. A daily dose of 200 mg/day has inconsistent effects and is less effective than 400 mg/day. It is recommended that therapy be initiated at 50 mg/day followed by titration to an effective dose. Daily doses above 1,600 mg have not been studied.

The recommended titration rate for topiramate is:

	AM DOSE	PM DOSE
Week 1	none	50 mg
Week 2	50 mg	50 mg
Week 3	50 mg	100 mg
Week 4	100 mg	100 mg
Week 5	100 mg	150 mg
Week 6	150 mg	150 mg
Week 7	150 mg	200 mg
Week 8	200 mg	200 mg

It is not necessary to monitor topiramate plasma concentrations to optimize TOPAMAX® therapy. On occasion, the addition of TOPAMAX® to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX® may require adjustment of the dose of TOPAMAX®.

Table 5: Incidence (%) of Dose-Related Adverse Events From Five Placebo-Controlled, Add-On Trials

Adverse Event	TOPAMAX® Dosage (mg/day)		
	Placebo (N=174)	200 (N=45)	400 (N=68)
Fatigue	14.4	11.1	11.8
Nervousness	7.5	13.3	17.6
Difficulty with Concentration/Attention	1.1	6.7	8.8
Confusion	5.2	8.9	10.3
Depression	6.3	8.9	7.4
Anorexia	4.0	4.4	5.9
Language problems	0.6	2.2	8.8
Anxiety	5.2	2.2	2.9
Mood problems	1.7	0.0	5.9
Cognitive problems NOS	0.6	0.0	0.0
Weight decrease	2.3	4.4	8.8
Tremor	6.3	13.3	8.8

small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

Patients with Renal Impairment:

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m²), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

Patients Undergoing Hemodialysis:

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

Patients with Hepatic Disease:

In hepatically impaired patients topiramate plasma concentrations may be increased. The mechanism is not well understood.

HOW SUPPLIED

TOPAMAX® (topiramate capsules) Sprinkle Capsules contain small, white to off-white spheres. The gelatin capsules are white and clear.

They are marked as follows:

15 mg capsules with "TOP" and "15 mg" on the side.

25 mg capsules with "TOP" and "25 mg" on the side.

The capsules are supplied as follows:

15 mg capsules bottles of 60 (NDC 0045-0647-65)

25 mg capsules bottles of 60 (NDC 0045-0645-65)

TOPAMAX® (topiramate capsules) Sprinkle Capsules should be stored in tightly-closed containers at or below 25°C (77°F). Protect from moisture.

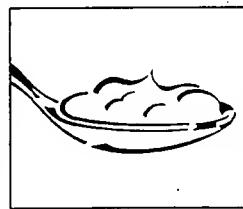
TOPAMAX® (topiramate capsules) is a trademark of OMP DIVISION, ORTHO-MCNEIL PHARMACEUTICAL, INC.

HOW TO TAKE TOPAMAX® (topiramate capsules)

SPRINKLE CAPSULES

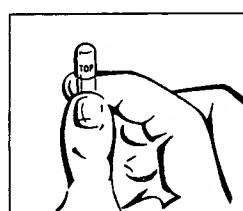
A Guide for Patients and Their Caregivers

Your doctor has given you a prescription for TOPAMAX® (topiramate capsules) Sprinkle Capsules. Here are your instructions for taking this medication. Please read these instructions prior to use.



To Take With Food

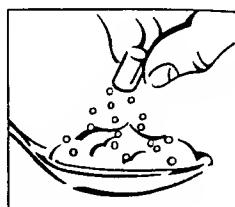
You may sprinkle the contents of TOPAMAX® Sprinkle Capsules on a small amount (teaspoon) of soft food, such as applesauce, custard, oatmeal, ice cream, yogurt, or pudding.



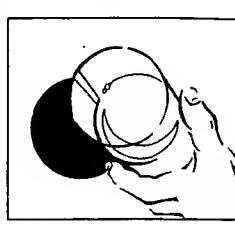
Hold the capsule upright so that you can read the word "TOP".



Carefully twist off the clear portion of the capsule. You may find it best to do this over the small portion of the food onto which you will be pouring the



Sprinkle all of the capsule's contents onto a spoonful of soft food. Take care not to spill the capsule. Taking care of the entire capsule's contents onto the food is also important.



Be sure the capsule is swallowed. This can be done by spoonfuls of the food/meal/soft food mixture immediately. If capsules should be swallowed, this may be helpful. If the patient cannot swallow immediately in order to make sure all of the capsule's contents are taken. IMPORTANT: Do not store any sprinkle capsules for later time.

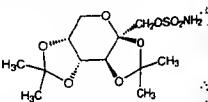
TOPAMAX®

[tō'pō-māks]
(topiramate) tablets

DESCRIPTION

TOPAMAX® (topiramate) is a sulfamate-substituted monosaccharide that is intended for use as an antiepileptic. It is available as 25 mg, 100 mg, and 200 mg round tablets for oral administration.

Topiramate is a white crystalline powder with a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, and methanol, and is sparingly soluble in water, 95% ethanol, and 1,4-dioxane. Its saturated solution has a pH of 6.3. Topiramate has the molecular formula C₁₂H₂₂NO₆S and a molecular weight of 339.36. Topiramate is designated chemically as bis-O-(1-methyllethylene)-β-D-fructopyranose sulfamate and has the following structural formula:



TOPAMAX® (topiramate) Tablets contain the following active ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hypromellose, propyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide (100 and 200 mg tablets), sorbitol 80.

CLINICAL PHARMACOLOGY

Mechanism of Action:

The precise mechanism by which topiramate exerts its antiepileptic effect is unknown; however, electrophysiological and biochemical studies of the effects of topiramate on cultured neurons have revealed three properties that may contribute to topiramate's antiepileptic efficacy. First, topiramate may reduce the frequency and/or amplitude of sustained depolarizations.

enhances the ability of GABA to induce a flux into neurons, suggesting that topiramate increases the activity of this inhibitory neurotransmitter. It is not blocked by flumazenil, a benzodiazepine antagonist. Topiramate increases the duration of the GABA_A response, differentiating topiramate from barbiturates, which modulate GABA_A receptors. Third, topiramate increases the ability of kainate to activate the kainate/2-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) subtype of excitatory amino acid (glutamate) receptors. Topiramate has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtypes. The effect of topiramate on concentration-dependent inhibition is concentration-dependent, in the range of 1 μ M to 200 μ M.

Topiramate inhibits some isoenzymes of carbonic anhydrase (CA-IV). This pharmacologic effect is greater than that of acetazolamide, a known carbonic anhydrase inhibitor, and is not thought to be a major contribution to topiramate's antiepileptic activity.

Topiramate has anticonvulsant activity in rat and mouse models of partial and generalized tonic-clonic (grand mal) seizures (MES) tests. Topiramate is also effective in blocking clonic seizures induced by the receptor antagonist, pentylenetetrazole. Topiramate is effective in rodent models of epilepsy, which include absence-like seizures in the spontaneous epileptic rat, and tonic and clonic seizures induced in the amygdala or by global ischemia.

Topiramate is rapidly absorbed, with peak plasma concentrations occurring at approximately 2 hours following a 400 mg oral dose. The relative bioavailability of topiramate from oral tablets is about 80% compared to a solution. The bioavailability of topiramate is not affected by food. The pharmacokinetics of topiramate are linear with dose. Increases in plasma concentration over the dose range of 200 to 800 mg/day. The mean plasma half-life is 21 hours after single or multiple doses. The half-life is thus reached in about 4 days in patients with normal renal function. Topiramate is 13-17% bound to plasma proteins over the concentration range of 0-1000 μ g/ml.

Topiramate Excretion: Topiramate is extensively metabolized and is primarily excreted unchanged in the urine (approximately 70% of a single dose). Six metabolites have been identified, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation and glucuronidation. There is evidence for active tubular reabsorption of topiramate. In rats, given topiramate, active tubular reabsorption, along with topiramate increase in renal clearance of topiramate. This interaction has not been evaluated in humans. Overall, plasma clearance is approximately 200 mL/min following oral administration.

Drug Interactions (see also Drug Interactions): There are no interactions between topiramate and standard AEDs. There are, however, in controlled clinical pharmacokinetic studies with epilepsy. The effect of these interactions on plasma AUCs are summarized under PRECAUTIONS.

Topiramate clearance was reduced by 42% in moderately impaired subjects (creatinine clearance 30-69 mL/min) and 45% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m²) compared to normal subjects (creatinine clearance >70 mL/min). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this will be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease may affect glomerular filtration rate and tubular secretion, resulting in a clearance of topiramates not proportional to creatinine clearance. In general, however, use of a reduced dose is recommended in patients with severe renal impairment.

Topiramate is cleared by hemodialysis. Using a high efficiency, single-pass-dialysate hemodialysis procedure, dialysate clearance was 120 mL/min with a dialyzer flow rate of 400 mL/min. This high flow rate is 20-30 mL/min total oral clearance (while dialysis will remove a clinically significant amount from the patient over the hemodialysis period). Therefore, a dose adjustment may be necessary.

DOSE AND ADMINISTRATION

In impaired subjects, the clearance of topiramate is decreased; the mechanism underlying the decrease is not understood.

Race: Topiramate was not affected by age (18-67 years).

Pharmacokinetics: The pharmacokinetics of topiramate were evaluated in patients receiving one or two other antiepileptic drugs. No differences in pharmacokinetic profiles were obtained after one

Table 1: Topiramate Dose Summary During the Stabilization Periods of Each of Five Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Stabilization Dose	Placebo ^a	Target Topiramate Dosage (mg/day)				
			200	400	600	800	1,000
YD	N	42	42	40	41	41	41
	Mean Dose	5.9	200	390	556	739	796
	Median Dose	6.0	200	400	600	800	1,000
YE	N	44	44	40	45	40	40
	Mean Dose	9.7	—	544	739	796	—
	Median Dose	10.0	—	600	800	1,000	—
Y1	N	23	19	—	—	—	—
	Mean Dose	3.8	395	—	—	—	—
	Median Dose	4.0	400	—	—	—	—
Y2	N	30	—	28	—	—	—
	Mean Dose	5.7	—	522	—	—	—
	Median Dose	6.0	—	600	—	—	—
Y3	N	28	—	25	—	—	—
	Mean Dose	7.9	—	568	—	—	—
	Median Dose	8.0	—	600	—	—	—

^aPlacebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol Y1, 4 tablets/day; Protocols YD and Y2, 6 tablets/day; Protocol Y3, 8 tablets/day.

Table 2: Median Percent Seizure Rate Reduction and Percent Responders in Five Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Efficacy Result	Placebo	Target Topiramate Dosage (mg/day)				
			200	400	600	800	1,000
YD	N	45	45	45	46	46	46
	Median % Reduction	11.6	27.2 ^a	47.5 ^b	44.7 ^c	44.7 ^c	44.7 ^c
	% Responders	18	24	44 ^d	46 ^d	46 ^d	46 ^d
YE	N	47	—	—	48	48	47
	Median % Reduction	1.7	—	40.8 ^e	41.0 ^e	36.0 ^e	36.0 ^e
	% Responders	9	—	40 ^f	41 ^f	36 ^f	36 ^f
Y1	N	24	23	—	—	—	—
	Median % Reduction	1.1	40.7 ^g	—	—	—	—
	% Responders	8	35 ^g	—	—	—	—
Y2	N	30	—	80	—	—	—
	Median % Reduction	12.2	—	46.4 ^h	—	—	—
	% Responders	10	—	47 ^h	—	—	—
Y3	N	28	—	28	—	—	—
	Median % Reduction	20.6	—	24.3 ^h	—	—	—
	% Responders	10	—	43 ^h	—	—	—

Comparisons with placebo: ^ap = 0.080; ^bp ≤ 0.010; ^cp ≤ 0.001; ^dp ≤ 0.050; ^ep = 0.065; ^fp ≤ 0.005.

CLINICAL STUDIES

The effectiveness of topiramate as an adjunctive treatment for partial onset seizures was established in five, multicenter, randomized, double-blind, placebo-controlled trials, two comparing several dosages of topiramate and placebo and three comparing single dosage with placebo, in patients with a history of partial onset seizures, with or without secondarily generalization.

Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® or placebo. In each study, patients were stabilized on optimum dosages of their concomitant AEDs during an 8-12 week baseline phase. Patients who experienced at least 12 (or 8, for 8-week baseline studies) partial onset seizures, with or without secondarily generalization, during the baseline phase were randomly assigned to placebo or a specified dose of TOPAMAX® in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. After titration, patients entered an 8 or 12-week stabilization period. The numbers of patients randomized to each dose, and the actual mean, and median doses in the stabilization period are shown in Table 1.

[See table 1 above]

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. Responder rate (fraction of patients with at least a 50% reduction) was also measured. The median percent reductions in seizure rates and the responder rates by treatment group for each study are shown in Table 2.

[See table 2 above]

Subset analyses of the antiepileptic efficacy of TOPAMAX® in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

INDICATIONS AND USAGE

TOPAMAX® (topiramate) is indicated as adjunctive therapy for the treatment of adults with partial onset seizures.

CONTRAINDICATIONS

TOPAMAX® (topiramate) is contraindicated in patients with a history of hypersensitivity to any component of this

Cognitive/Neuropsychiatric Adverse Events

Adverse events most often associated with the use of TOPAMAX® were central nervous system-related. The most significant of these can be classified into two general categories: 1) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties and 2) somnolence or fatigue. Additional nonspecific CNS effects occasionally observed with topiramate as add-on therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances (e.g., irritability and depression).

Reports of psychomotor slowing, speech and language problems, and difficulty with concentration and attention were common. Although in some cases these events were mild to moderate, they at times led to withdrawal from treatment. The incidence of psychomotor slowing is only marginally dose-related, but both language problems and difficulty with concentration or attention clearly increased in frequency with increasing dosage in the five double-blind trials [see ADVERSE REACTIONS, Table 5].

Somnolence and fatigue were the most frequently reported adverse events during clinical trials with TOPAMAX®. These events were generally mild to moderate and occurred early in therapy. While the incidence of somnolence does not appear to be dose-related, that of fatigue increases at doses above 400 mg/day.

Sudden Unexplained Death in Epilepsy (SUDEP)

During the course of premarketing development of TOPAMAX® (topiramate), 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2,796 subject-years of exposure).

This represents an incidence of 0.0035 deaths per patient per year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving TOPAMAX (ranging from 0.0005 for the general population of patients with epilepsy, to 0.003 for a clinical trial population similar to that in the TOPAMAX program, to 0.005 for patients with refractory epilepsy).

PRECAUTIONS

General:

Kidney Stones:

A total of 322,086 (1.5%) of patients exposed to topiramate during its development reported the occurrence of kidney

Topamax—Cont.

An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a weak carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of TOPAMAX® with other carbonic anhydrase inhibitors may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

Paresthesia

Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®.

Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required (see DOSAGE AND ADMINISTRATION).

Decreased Hepatic Function

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.

Information for Patients:

Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation (see PRECAUTIONS: General, for support regarding hydration as a preventative measure).

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

Drug Interactions:**Antiepileptic Drugs**

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized in the following table:

In Table 3, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added.

The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX® was given alone.

Table 3: Summary of AED Interactions with TOPAMAX®

AED	AED Co-administered	Concentration increase ^a	Topiramate Concentration decrease ^a
Phenytoin		NC or 25%	48% decrease
Carbamazepine (CBZ)	NC		40% decrease
CBZ epoxide ^b	NC		NE
Valproic acid	11% decrease		14% decrease
Phenobarbital	NC		NE
Primidone	NC		NE

^a = Plasma concentration increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin.

^b = is not administered but is an active metabolite of carbamazepine.

NC = Less than 10% change in plasma concentration.

AED = Antiepileptic drug.

NE = Not evaluated.

Other Drug Interactions

Digoxin: In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established.

CNS Depressants: Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants.

Ovaral Contraceptives: In an interaction study with oral contraceptives using a combination product containing norethindrone and ethinyl estradiol, TOPAMAX® did not significantly affect the clearance of norethindrone. The mean total exposure to the estrogenic component decreased by 18%, 21%, and 30% at daily doses of 200, 400, and 800 mg/day, respectively. Therefore, efficacy of oral contraceptives may be compromised by topiramate. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns. The effect of oral contraceptives on the pharmacokinetics of topiramate is not known.

Others: Concomitant use of TOPAMAX®, a weak carbonic

Table 4: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials^{a,b} (Events that occurred in at least 1% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients)

Body System/ Adverse Event ^c	TOPAMAX® Dosage (mg/day)		
	Placebo (N=174)	200-400 (N=113)	600-1,000 (N=74)
Body as a Whole - General Disorders			
Asthenia	1.1	8.0	4.1
Back Pain	4.0	6.2	4.1
Chest Pain	2.3	4.4	2.0
Influenza-Like Symptoms	2.9	3.5	2.0
Leg Pain	2.3	3.5	3.2
Hot Flushes	1.7	2.7	2.1
Body Odor	0.0	1.8	0.6
Edema	1.1	1.8	0.0
Rigors	0.0	1.8	0.0
Central & Peripheral Nervous System Disorders			
Dizziness	14.4	28.3	32.1
Ataxia	6.9	21.2	17.0
Speech Disorders/ Related Speech Problems	2.9	16.8	13.8
Nystagmus	11.5	15.0	15.0
Paresthesia	3.4	15.0	14.5
Tremor	6.3	10.6	13.8
Language Problems	0.6	6.2	11.7
Coordination Abnormal	1.7	5.3	3.6
Hypoesthesia	1.1	2.7	0.8
Gastrointestinal System Disorders			
Nausea	6.3	11.5	13.8
Dyspepsia	5.2	8.0	5.7
Abdominal Pain	2.9	5.3	7.3
Constipation	0.6	5.3	3.2
Dry Mouth	1.1	2.7	3.2
Gingivitis	0.0	1.8	0.4
Hearing and Vestibular Disorders			
Hearing Decreased	1.1	1.8	1.6
Metabolic and Nutritional Disorders			
Weight Decrease	2.3	7.1	12.6
Musculoskeletal System Disorders			
Myalgia	1.1	1.8	1.2
Platelet, Bleeding and Clotting Disorders			
Epistaxis	1.1	1.8	0.8
Psychiatric Disorders			
Somnolence	10.3	30.1	25.9
Psychomotor Slowing	2.3	16.8	25.1
Nervousness	7.5	15.9	20.6
Difficulty with Memory	2.9	12.4	12.6
Confusion	5.2	9.7	15.0
Depression	6.3	8.0	13.4
Difficulty with Concentration/Attention	1.1	8.0	15.1
Anorexia	4.0	5.3	11.3
Agitation	1.7	4.4	4.0
Mood Problems	1.7	3.5	10.1
Aggressive Reaction	0.6	2.7	4.0
Apathy	0.0	1.8	4.6
Depersonalization	0.6	1.8	1.6
Emotional Lability	1.1	1.8	2.1
Reproductive Disorders, Female			
Breast Pain, Female	0.0	8.3	0.0
Dysmenorrhea	2.6	8.3	0.0
Menstrual Disorder	0.0	4.2	0.0
Respiratory System Disorders			
Upper Respiratory Infection	11.5	12.4	12.1
Pharyngitis	2.9	7.1	2.8
Sinusitis	4.0	4.4	4.0
Dyspnea	1.1	1.8	3.2
Skin and Appendages Disorders			
Rash	4.0	4.4	3.2
Pruritus	1.1	1.8	3.2
Sweating Increased	0.0	1.8	0.4
Urinary System Disorders			
Hematuria	0.6	1.8	0.8
Vision Disorders			
Diplopia	6.3	14.2	14.5
Vision Abnormal	2.9	14.2	10.5
Eye Pain	1.1	1.8	2.0
White Cell and Res Disorders			
Leukopenia	0.6	2.7	1.6

^a Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX®.

^b Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

^c Adverse events reported by at least 1% of patients in the TOPAMAX 200-400 mg/day group and more common than placebo group are listed in this table.

Laboratory Tests: There are no known interactions of topiramate with commonly used laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300

mg/kg, was not statistically significant in males and females receiving 20 mg/kg. The relevance of this finding to human carcinogenicity is not known. No evidence of carcinogenicity was seen in a 2-year study in rats following oral administration of topiramate for 100, 200, and 400 mg/kg/day.

Table 5. Incidence (%) of Dose-Related Adverse Events From Five Placebo-Controlled, Add-On Trials

Adverse Event	TOPAMAX® Dosage (mg/day)			
	Placebo (N=174)	200 (N=45)	400 (N=68)	600-1,000 (N=247)
Fatigue	14.4	11.1	11.8	30.8
Nervousness	7.5	13.3	17.6	20.6
Difficulty with Concentration/Attention	1.1	6.7	8.8	15.4
Confusion	5.2	8.9	10.3	15.0
Depression	6.3	8.9	7.4	13.4
Anorexia	4.0	4.4	5.9	11.3
Language problems	0.6	2.2	8.8	11.7
Anxiety	5.2	2.2	2.9	9.3
Mood problems	1.7	0.0	5.9	10.1
Cognitive problems NOS	0.6	0.0	0.0	4.0
Weight decrease	2.3	4.4	8.8	12.6
Tremor	6.3	13.3	8.8	13.8

guage problems, anxiety, mood problems, cognitive problems not otherwise specified, weight decreased, and tremor [see Table 5].

In controlled clinical trials, 11% of patients receiving topiramate 200 to 400 mg/day as adjunctive therapy discontinued due to adverse events. This rate appeared to increase at dosages above 400 mg/day. Adverse events associated with discontinuing therapy included somnolence, dizziness, anxiety, difficulty with concentration or attention, fatigue, and paresthesia and increased at dosages above 400 mg/day. Approximately 28% of the 1,715 individuals with epilepsy who received topiramate at dosages of 200 to 1,600 mg/day in clinical studies discontinued treatment because of adverse events; an individual patient could have reported more than one adverse event. These adverse events were: psychomotor slowing (4.1%), difficulty with memory (3.3%), fatigue (3.3%), confusion (3.2%), somnolence (3.2%), difficulty with concentration/attention (2.9%), anorexia (2.9%), depression (2.6%), dizziness (2.6%), weight decrease (2.5%), nervousness (2.2%), ataxia (2.2%), paresthesia (2.0%), and language problems (2.0%).

Incidence in Controlled Clinical Trials - Add-On Therapy
Table 4 lists treatment-emergent adverse events that occurred in at least 1% of patients treated with 200 to 400 mg/day topiramate in controlled trials that were numerically more common at this dose than in the patients treated with placebo. In general, most patients who experienced adverse events during the first eight weeks of these trials no longer experienced them by their last visit.

The prescriber should be aware that these data were obtained when TOPAMAX® was added to concurrent antiepileptic drug therapy and cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with data obtained from other clinical investigations involving different treatments, uses, or investigators. Inspection of these frequencies, however, does not provide the prescribing physician with basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

[See Table 4 at top of previous page]

[See Table 5 above]

Other Adverse Events Observed

Other events that occurred in more than 1% of patients treated with 200 to 400 mg of topiramate in placebo-controlled trials but with equal or greater frequency in the placebo group were: fatigue, headache, injury, anxiety, rash, pain, convulsions aggravated, coughing, gastroenteritis, rhinitis, back pain, hot flushes, bronchitis, abnormal gait, involuntary muscle contractions, and epistaxis.

Other Adverse Events Observed During All Clinical Trials

Topiramate, initiated as adjunctive therapy, has been administered to 1,715 patients with epilepsy during all clinical studies. During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. The frequencies presented represent the proportion of 1,715 topiramate-treated patients who experienced an event of the type cited on at least one occasion while receiving topiramate. Reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* occurring in at least 1/100 patients; *infrequent* occurring in 1/100 to 1/1000 patients; *rare* occurring in fewer than 1/1000 patients.

Autonomic Nervous System Disorders: *Infrequent:* vasodilation.

Body as a Whole: *Frequent:* fatigue, fever, malaise. *Infrequent:* syncope, halitosis, abdomen enlarged. *Rare:* alcohol intolerance, substernal chest pain, sudden death.

Cardiovascular Disorders, General: *Infrequent:* hypertension, hypotension, postural hypotension.

Central & Peripheral Nervous System Disorders: *Frequent:* hypokinesia, vertigo, stupor, convulsions grand mal, hyperkinesia, hypertension. *Infrequent:* leg cramps, hyporeflexia.

field defect, coma, encephalopathy, fecal incontinence, upper motor neuron lesion. *Rare:* cerebellar syndrome, EEG abnormal, tongue paralysis.

Endocrine Disorders: *Infrequent:* goiter. *Rare:* thyroid disorder.

Gastrointestinal System Disorders: *Frequent:* diarrhea, vomiting, flatulence, gastroenteritis. *Infrequent:* gum hyperplasia, hemorrhoids, tooth caries, stomatitis, dysphagia, melena, gastritis, saliva increased, hiccup, gastroesophageal reflux, tongue edema, esophagitis. *Rare:* eructation.

Hearing and Vestibular Disorders: *Frequent:* tinnitus. *Rare:* earache, hyperacusis.

Heart Rate and Rhythm Disorders: *Frequent:* palpitation. *Infrequent:* AV block bradycardia, bundle branch block. *Rare:* arrhythmia, arrhythmia atrial, fibrillation atrial.

Liver and Biliary System Disorders: *Infrequent:* SGPT increased, SGOT increased, gall bladder disorder. *Rare:* gamma-GT increased.

Metabolic and Nutritional Disorders: *Frequent:* weight increase. *Infrequent:* thirst, hypokalemia, alkaline phosphatase increased, dehydration, hypocalcemia, hyperlipemia, acidosis, hyperglycemia, creatinine increased, hyperchloremia, xerophthalmia. *Rare:* diabetes mellitus, hypernatremia, abnormal serum folate, hyponatremia, hypcholesterolemia, hypoglycemia, hypophosphatemia.

Musculoskeletal System Disorders: *Frequent:* arthralgia, muscle weakness. *Infrequent:* arthrosis, osteoporosis.

Myo-, Endo-, Paricardial & Valva Disorders: *Infrequent:* angina pectoris.

Neoplasms: *Infrequent:* basal cell carcinoma, thrombocythemia. *Rare:* polycythemia.

Platelet, Bleeding, and Clotting Disorders: *Infrequent:* gingival bleeding, purpura, thrombocytopenia, pulmonary embolism.

Psychiatric Disorders: *Frequent:* insomnia, personality disorder, impotence, hallucination, euphoria, psychosis, libido decreased, suicide attempt. *Infrequent:* paranoid reaction, appetite increased, delusion, paranoia, delirium, abnormal dreaming, neurosis. *Rare:* libido increased, manic reaction.

Red Blood Cell Disorders: *Frequent:* anemia. *Rare:* marrow depression, pancytopenia.

Reproductive Disorders, Female: *Frequent:* intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis, amenorrhea. *Reproductive Disorders, Male:* *Infrequent:* ejaculation disorder, breast discharge.

Respiratory System Disorders: *Frequent:* coughing, bronchitis. *Infrequent:* asthma, bronchospasm. *Rare:* laryngismus.

Skin and Appendages Disorders: *Frequent:* acne, alopecia. *Infrequent:* dermatitis, nail disorder, folliculitis, dry skin, urticaria, skin discoloration, eczema, photosensitivity reaction, erythematous rash, seborrhea, sweating decreased, abnormal hair texture. *Rare:* chloasma.

Special Senses Other Disorders: *Frequent:* taste perversion. *Infrequent:* taste loss, parosmia.

Urinary System Disorders: *Frequent:* urinary tract infection, micturition frequency, urinary incontinence, dysuria, renal calculi. *Infrequent:* urinary retention, face edema, renal pain, nocturia, albuminuria, polyuria, oliguria.

Vascular (Extracardiac) Disorders: *Infrequent:* flushing, deep vein thrombosis, phlebitis. *Rare:* vasospasm.

Vision Disorders: *Frequent:* conjunctivitis. *Infrequent:* abnormal accommodation, photophobia, abnormal lacrimation, strabismus, color blindness, myopia, mydriasis. *Rare:* cataract, corneal opacity, iritis.

White Cell and Reticuloendothelial System Disorders: *Infrequent:* lymphadenopathy, eosinophilia, lymphopenia, granulocytopenia, lymphocytosis.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of TOPAMAX® (topiramate) has not been evaluated in human studies.

OVERDOSAGE

In acute TOPAMAX® (topiramate) overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has not been shown to adsorb topiramate *in vitro*. Therefore, its use in overdose is not recommended. Treatment should be ap-

Topamax—Cont.

properly supportive. Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdosage reported, hemodialysis has not been necessary.

DOSAGE AND ADMINISTRATION

In the controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and clinical efficacy. No evidence of tolerance has been demonstrated in humans. Doses above 400 mg/day (600, 800, and 1000 mg/day) have not been shown to improve responses.

The recommended total daily dose of TOPAMAX® (topiramate) as adjunctive therapy is 400 mg/day in two divided doses. A daily dose of 200 mg/day has inconsistent effects and is less effective than 400 mg/day. It is recommended that therapy be initiated at 50 mg/day followed by titration to an effective dose. Daily doses above 1,600 mg have not been studied.

The recommended titration rate for topiramate is:

	AM DOSE	PM DOSE
Week 1	none	50 mg
Week 2	50 mg	50 mg
Week 3	50 mg	100 mg
Week 4	100 mg	100 mg
Week 5	100 mg	150 mg
Week 6	150 mg	150 mg
Week 7	150 mg	200 mg
Week 8	200 mg	200 mg

It is not necessary to monitor topiramate plasma concentrations to optimize TOPAMAX® therapy. On occasion, the addition of TOPAMAX® to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX® may require adjustment of the dose of TOPAMAX®. Because of the bitter taste, tablets should not be broken. TOPAMAX® can be taken without regard to meals.

Patients with Renal Impairment:

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m²), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

Patients Undergoing Hemodialysis:

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

Patients with Hepatic Disease:

In hepatically impaired patients topiramate plasma concentrations may be increased. The mechanism is not well understood.

HOW SUPPLIED

TOPAMAX® (topiramate) is available as debossed, coated, round tablets in the following strengths and colors: 25 mg white (coded "TOP" on one side; "25" on the other) 100 mg yellow (coded "TOPAMAX" on one side; "100" on the other)

200 mg salmon (coded "TOPAMAX" on one side; "200" on the other)

They are supplied as follows:

25 mg tablets - bottles of 60 count with desiccant (NDC 0045-0639-65)

100 mg tablets - bottles of 60 count with desiccant (NDC 0045-0641-65)

200 mg tablets - bottles of 60 count with desiccant (NDC 0045-0642-65)

TOPAMAX® (topiramate) Tablets should be stored in tightly-closed containers at controlled room temperature, (59 to 86°F, 15 to 30°C). Protect from moisture.

TOPAMAX® (topiramate) is a trademark of OMP DIVISION, ORTHO-MCNEIL PHARMACEUTICAL, INC.

Raritan, NJ 08869

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Shown in Product Identification Guide, page 329

TYLENOL® with Codaina
[ti 'len-əu-lə co 'dēn]

(acetaminophen and codaine phosphate tablets and oral solution USP)

Tablets® and Elixir®

Analgesic For Oral Use

No. 3-NSN 6505-00-400-2054—100's

No. 3-NSN 6505-00-147-8347—500's

No. 3-NSN 6505-01-086-2993—U/D 500's

No. 3-NSN 6505-00-372-3032—1000's

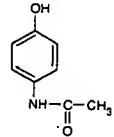
Elixir-NSN 6505-01-035-1963—Pints

No. 3 Codeine Phosphate*	30 mg
Acetaminophen	300 mg
No. 4 Codeine Phosphate*	60 mg
Acetaminophen	300 mg
Elixir 5 mL of elixir contains:	
Codeine Phosphate*	12 mg
Acetaminophen	120 mg
Alcohol	7%

*Warning—May be habit forming.

Inactive ingredients: tablets—powdered cellulose, magnesium stearate, sodium metabisulfite, pregelatinized starch, starch (corn); elixir—sucrose, citric acid, propylene glycol, sodium benzoate, saccharin sodium, sucrose, natural and artificial flavors, FD&C Yellow No. 6.

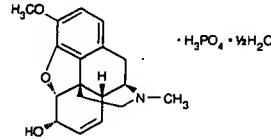
Acetsminophen, 4'-hydroxycetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. Its structure is as follows:



C₈H₉NO

M.W. 151.16

Codeine is an alkaloid, obtained from opium or prepared from morphine by methylation. Codeine phosphate occurs as fine, white, needle-shaped crystals, or white, crystalline powder. It is affected by light. Its chemical name is: 7,8-didehydro- 4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate. Its structure is as follows:



C₁₈H₂₁NO₃PO₄ · ½H₂O

M.W. 406.37

†See WARNINGS

CLINICAL PHARMACOLOGY

TYLENOL with Codeine (acetaminophen and codeine phosphate tablets and oral solution USP) combine the analgesic effects of a centrally acting analgesic, codeine, with a peripherally acting analgesic, acetaminophen. Both ingredients are well absorbed orally. The plasma elimination half-life ranges from 1 to 4 hours for acetaminophen, and from 2.5 to 3 hours for codeine.

Codeine retains at least one-half of its analgesic activity when administered orally. A reduced first-pass metabolism of codeine by the liver accounts for the greater oral efficacy of codeine when compared to most other morphine-like narcotics. Following absorption, codeine is metabolized by the liver and metabolic products are excreted in the urine. Approximately 10 percent of the administered codeine is demethylated to morphine, which may account for its analgesic activity.

Acetaminophen is distributed throughout most fluids of the body, and is metabolized primarily in the liver. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

INDICATIONS AND USAGE

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) are indicated for the relief of mild to moderately severe pain.

TYLENOL with Codeine elixir (acetaminophen and codeine phosphate oral solution USP) is indicated for the relief of mild to moderate pain.

CONTRAINDICATIONS

TYLENOL with Codeine tablets or elixir (acetaminophen and codeine phosphate tablets and oral solution USP) should not be administered to patients who have previously exhibited hypersensitivity to any component.

WARNINGS

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS**General**

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exag-

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis and course of patients with acute abdominal conditions. **Special Risk Patients:** This drug should be given with caution to certain patients such as the elderly, debilitated, and those with severe impairment of hepatic or renal function, hypertension, hypothyroidism, Addison's disease, and peripheral neuropathy or urethral stricture.

Information for Patients

Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient should be cautioned accordingly. The patient should understand the single-dose and 24-hour dose limits, and the time interval between doses.

Drug Interactions

Patients receiving other narcotic analgesics, antihistamines, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with this drug may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced. The coadministration of anticholinergics with codeine may produce paralytic ileus.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed with acetaminophen or codeine to determine carcinogenic potential or effects on fertility.

Acetaminophen and codeine have been found to have mutagenic potential using the Ames Salmonella-Microsome Activation test, the Basc test on Drosophila melanogaster, and the Micronucleus test on mouse bone marrow.

Pregnancy

Teratogenic Effects: Pregnancy Category C. Codeine: A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rats at the 120 mg/kg level, in the toxic range for the animal, were associated with an increase in embryo resorption at the time of implantation. In another study a single 100 mg/kg dose of codeine administered to pregnant rats reportedly resulted in delayed ossification in the offspring. There are no studies in humans, and the significance of these findings to humans, if any, is not known.

TYLENOL with Codeine (acetaminophen and codeine phosphate tablets and oral solution USP) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:

Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Withdrawal signs include irritability, excessive crying, tremors, hyperactivity, fever, vomiting, and diarrhea. These signs usually appear during the first few days of life.

Labor and Delivery

Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see OVERDOSAGE). The effect of codeine, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

Some studies, but not others, have reported detectable amounts of codeine in breast milk. The levels are probably not clinically significant after usual therapeutic doses. The possibility of clinically important amounts being excreted in breast milk in individuals abusing codeine should be considered.

Pediatric Use

Safe dosage of TYLENOL with Codeine elixir (acetaminophen and codeine phosphate oral solution USP) has not been established in children below the age of three years.

ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, shortness of breath, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include allergic reactions, euphoria, dysphoria, constipation, abdominal pain, and pruritus.

At higher doses, codeine has most of the disadvantages of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) are a Schedule III controlled substance.

TYLENOL with Codeine elixir (acetaminophen and codeine phosphate oral solution USP) is a Schedule V controlled substance.

Codeine can produce drug dependence of the morphine type, and, therefore, has the potential for being abused.

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